Late life depression

Sonnenberg, C.M.

2013

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LATE LIFE DEPRESSION:

SEX DIFFERENCES IN CLINICAL PRESENTATION AND MEDICATION USE

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CAROLINE SONNENBERG

The study presented in this thesis was conducted at the EMGO Institute for Health and Care Research (EMGO+), the department of Psychiatry (VU Medical Center Amsterdam) and the department of Sociology and Social Gerontology (Vrije Universiteit Amsterdam). EMGO+ participates in the Netherlands School of Primary Care Research (CaRe) which was re-acknowledged in 2005 by the Royal Netherlands Academy of Arts and Sciences (KNAW).

The study was funded by the Department of Psychiatry of the VU Medical Center Amsterdam and the Vrije Universiteit Amsterdam, and supported as well by research grants of the Universitair Stimuleringsfonds of the VU Amsterdam and SmithKlineBeecham, which are gratefully acknowledged.

Financial support for publication of this these was kindly provided by:
Department of Psychiatry, VU University Medical Center, Amsterdam
Vrije Universiteit, Amsterdam.

Department of Psychiatry

Lay-out, cover design and printing: Ipskamp Drukkers, Enschede, The Netherlands
Cover: Rogier van der Weyden (1400?-1464): fragment of The Seven Sacraments Triptych (ca 1440-1445). Antwerp, Koninklijk Museum voor Schone Kunsten.
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ISBN: 978-94-6191-866-6

VRIJE UNIVERSITEIT

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ACADEMISCH PROEFSCHRIFT

ter verkrijging van de graad Doctor aan
de Vrije Universiteit Amsterdam,
op gezag van de rector magnificus
prof.dr. F.A. van der Duyn Schouten,
in het openbaar te verdedigen
ten overstaan van de promotiecommissie
van de Faculteit der Geneeskunde
op maandag 14 oktober 2013 om 15.45 uur
in de aula van de universiteit,
De Boelelaan 1105

door

Caroline Margaretha Sonnenberg
geboren te Ouderkerk a/d Amstel

promotoren:	prof.dr. A.T.F. Beekman
	prof.dr. D.J.H. Deeg
copromotoren:	prof.dr. M.L. Stek
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Aan mijn ouders, Dick, Eveline, Tijmen en Marjolijn

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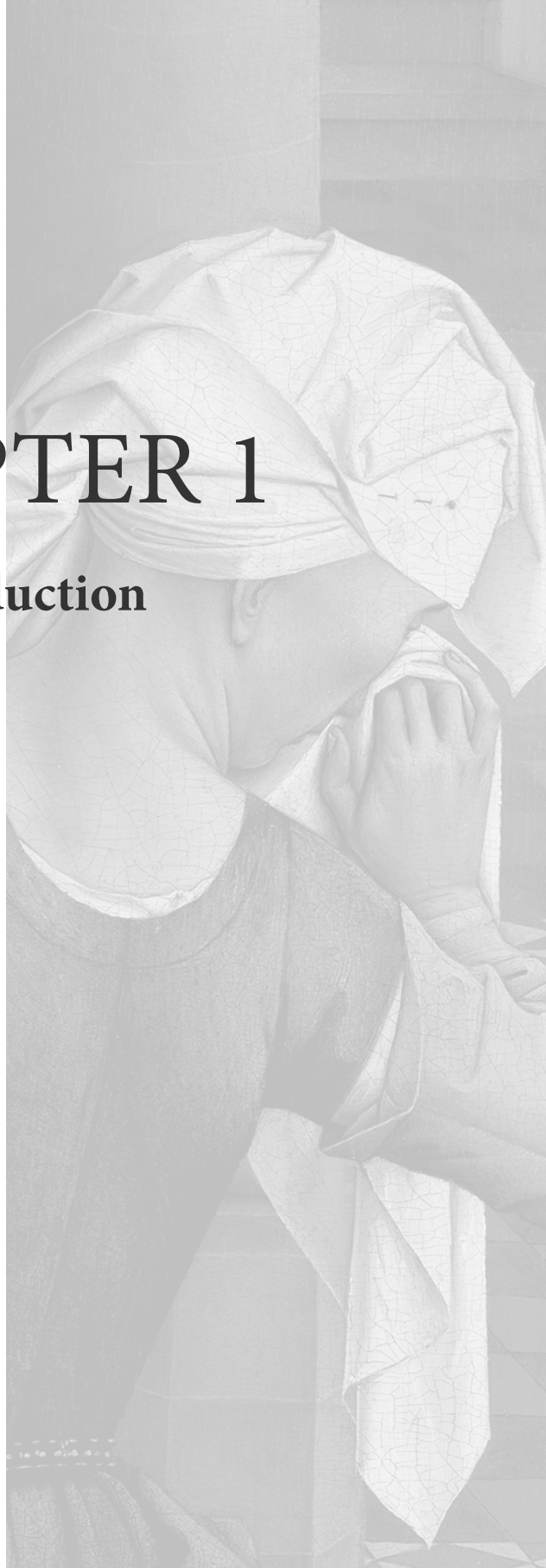


CHAPTER 1

Introduction

In the last century, life expectancy in the Western world has increased drastically, due to the improved sanitary conditions, the advances in the medical field, and the increased prosperity (Mackenbach 1996). The combination of this increasing life expectancy with the decline in birth rate has led to an increase of the proportion of people aged 65 years and older. In the Netherlands, for example, in 1950 7.7% of the population was 65 years or older. In 1990 this was 12.8%, in 2010 15.3% and for 2030 the expected rate is 23.8% (CBS - Statline 2012). Also the proportion of very old people (80 years and over) within this group is growing, with 22.7% in 1990, 25.5% in 2010 and an expectancy of 29.6% in the year 2030. The majority of them are women, particularly in the very old (65.8% in 2010), although this preponderance is expected to decrease to 59.5% in 2030 (CBS Statline 2012).

Aging brings about changes in social, cognitive, emotional and physical domains of functioning. Chronic physical diseases and functional disability often play a role, particularly over the age of 75. But also mental health problems may be a major issue, such as depression, anxiety, and cognitive problems or dementia. Both physical and mental health problems, but also psychosocial problems such as loss of important others or decrease of financial resources may lead to problems in autonomy and social functioning, to diminished quality of life, to an increased need for care by other persons (partner, family) and to an increased use of health care services.

The present thesis aims to investigate particular aspects of depression in later life: the role of gender, paying specific attention to religious background and social support, and medical treatment.

Depression

Depression is a major cause of disease-related disability in older as well as in younger adults. In 2004 depression was the second leading cause of non-fatal disease burden worldwide (WHO 2008). Since long depression is known as a condition of mental and physical disturbance, with lowered mood, loss of interest and motivation, and several physical problems such as sleep disturbances, loss of appetite and psychomotor symptoms (Jackson 1986). The emergence of depressive symptoms is thought to be the result of an interaction between internal and external factors: stress factors and endogenous/genetic, social and personality characteristics (Brown and Harris 1978). Depression shows a large heterogeneity in clinical presentation and severity, and often has serious and lasting negative consequences for mental, physical and social well-being (Wells, Stewart et al. 1989; Hays, Wells et al. 1995;

Beekman, Penninx et al. 1997; Charney, Reynolds et al. 2003). In the classification system of the DSM (Diagnostic and Statistical Manual of Mental Disorders) (American Psychiatric Association 2000) several types of unipolar affective disorders are distinguished, defined by a number of specific symptoms that must cause clinically significant distress or functional impairment (table 1). The Major Depressive Disorder (MDD) is defined by the almost continuous presence of five or more out of nine symptoms including one or both of the so-called A-criterion symptoms, depressed mood or diminished interest or pleasure, during at least two weeks. Dysthymia is defined as a chronically depressed mood most of the time during two years, with two or more out of six symptoms. For research reasons a minor or mild depression is defined. This is a subthreshold form of MDD, defined by the presence of two, three or four out of these nine symptoms. Despite the name, minor depression has shown clinical relevance and development to a major depressive episode (Meeks, Vahia et al.). In the literature, the term 'depression' or 'depressive syndrome' is often used, indicating the presence of clinically relevant depressive symptomatology (MDD or dysthymia or minor depression). This is in line with the increasing insight in the nature of depression as a broad concept with a great diversity in symptom patterns, severity, aetiology, course and risk factors. A dimensional approach seems to provide a better fit than the fixed sets of criteria In the DSM-IV.

Gender and depression

A striking feature of depression is gender difference. Life-time prevalence of depression in women (10-25%) is almost twice that in men (5-12%) (Weissman and Klerman 1977; Weissman 1987) (Kessler, McGonagle et al. 1993; Weissman, Bland et al. 1993; Bijl and Ravelli 2000; Marcus, Kerber et al. 2008; Seedat, Scott et al. 2009). This so-called gender gap is a robust finding, in developed and in developing countries. The gap emerges around the age of 14 and then persists across the life span (Byers, Yaffe et al. 2010; de Graaf, Ten Have et al. 2010). Gender differences are also found in the course of the depression and in symptom profiles. Women have higher relapse or non-remission rates, a larger number of episodes, more atypical symptoms, more suicide attempts, and they show more often a seasonal pattern. In women, comorbidity is more often found, particularly anxiety, somatoform disorders, bulimia and somatic disorders such as thyroid problems. In depressed men, comorbid alcohol and substance abuse are found more often than in women (Kuehner 2003; Marcus, Young et al. 2005; Marcus, Kerber et al. 2008).

Possible (partial) explanations of this gender disparity in depression have been put forward, concerning biological, psychological and socio-cultural domains. Biological explanations comprise gender differences in genes and gene-environment interaction, brain anatomy and function, and in neuro-endocrinologic functioning (Caspi, Sugden et al. 2003; Kendler, Kuhn et al. 2005; Kendler, Myers et al. 2005). The emergence of the gender gap during puberty and the association of depression with reproductive events, such as the menstrual cycle, pregnancy, postpartum period and menopause, suggest a relation of the gender gap with reproductive hormones. Indeed, estrogens have been found to have a differential effect on several parts of the stress system which may contribute to the gender difference in depression. Another neuro-endocrinologic sex difference has been found in the synthesis of serotonine, a neurotransmitter which is important in depression.

Psychological explanations of the gender gap focus on the psychological make-up of women (coping style, personality factors and personality disorders) that differs from that of men, and makes women more susceptible to the development of depressive symptoms. Women seem to be more prone to internalizing psychiatric disorders (e.g. depression and anxiety), whereas men are more prone to externalizing disorders (e.g. substance abuse and delinquent behaviour). Neuroticism is higher in females than in males (Goodwin and Gotlib 2004), women are found to ruminate more about negative experiences than men (Nolen-Hoeksema, Larson et al. 1999) and women show more behavioural inhibition and less behavioural drive than men, leading to an attitude of helplessness (Seligman 1972; Leach, Christensen et al. 2008). These factors were related to depression in women.

Socio-cultural explanations focus on socialization of girls, the (disadvantaged) social role and status and socio-economic position of women in society, life-events, role stress, victimization and social support. The gender role hypothesis asserts that gender differences in depression are due to differences in social position, stressors, coping resources and opportunities, which are all unequally divided among the genders regardless of space (different countries) and time (different generations). In a study of the WHO in 2009 in 15 countries all over the world, the gender gap showed narrowing in the younger age cohorts, associated with a steady decrease in female gender traditionality from the older to the younger cohorts in all countries (Seedat, Scott et al. 2009). Also gender specific role stress (multiple roles) is thought to contribute to women's higher rates in depression.

Gender differences in social support and social ties may contribute to the gender differences in depression. In general, interpersonal relationship seems to be of greater importance and impact for women than for men, with positive as well as negative consequences. Women report more support from friends than men, which is a protective factor against depression. However, having greater social network, also provides greater opportunity for negative interpersonal experiences (e.g. death of someone close) which may lead to depression (Kendler, Thornton et al. 2001; Leach, Christensen et al. 2008). Women feel more responsible in these relationships than men, which may lead to feelings of burden and overload (Neff and Karney 2005). In general, women report greater levels of stress in interpersonal relationships and in the family circle than men and this is associated with the gender differences in depression (Dalgard, Dowrick et al. 2006).

The last possible explanation is sought in artefactual effects and bias, such as help seeking behaviour, symptom reporting en diagnosing procedures. Women do indeed seek more help than men when they are depressed, and this may contribute to the preponderance of depression in women. However, not only in clinical studies, but also in population based studies, where help seeking does not play a role, the gender gap is found. Symptom reporting may be different in men and women. Men are found to report fewer symptoms with the same level of dysfunction, which may lead to not fulfilling the DSM-criteria, and some symptoms in rating scales are more often reported by women than by men (somatic symptoms, fatigue, anxiety). Sex differences in diagnosing depression are found to play a role, with doctors having a better recognition of depression in women than in men. Women show different illness behaviour than men, presenting more affective and emotional complaints. Besides, in males alcohol abuse may mask their underlying depression. Although these gender bias mechanisms may play a role, they explain only partially the gender differences in depression (Piccinelli and Wilkinson 2000).

Late life depression

In older adults, depression is one of the most prevalent psychiatric disorders. About 14% of the older population suffers from one or more periods of a depressive syndrome with clinical relevance (Blazer, Kessler et al. 1994; Beekman, Copeland et al. 1999; Beekman, Deeg et al. 2004). The prevalence and the incidence of depression seem to increase with age, although this increase may be due to physical diseases and functional impairment instead to age itself (Beekman, Deeg et al. 2001; Blazer 2010).

The diagnostic criteria of the DSM are considered to be too restricted for application in depressed older people. A system with levels of caseness has shown to be more useful, with separate levels of severity. According to this system, a depressive syndrome is defined, with several depressive symptoms, next to the major depressive disorder according to the DSM-IV, and already mentioned above as 'minor depression'.

The depressive syndrome is more frequent in older persons than the major depressive disorder (13% versus 2%), but the impact, also of this minor depression, on quality of life and psychosocial functioning is considerable. Mortality and somatic morbidity in both groups are higher than in the non-depressed older people, and they use more health care and non-mental health services (Beekman, Deeg et al. 1997).

Late life depression appears to be associated with several risk factors, e.g. the presence of chronic physical disease, functional limitations and diminished activity due to these physical problems (Geerlings, Beekman et al. 2000). This is a mutual relationship: physical problems are a risk factor for the incidence of depression, and older persons with a depression develop more often physical impairment when they have a chronic physical disease (Penninx, Guralnik et al. 1998; Penninx, Leveille et al. 1999; van Gool, Kempen et al. 2005) . Other important risk factors in late life depression are loss of the partner, lower socio-economic status (low level of income and education), low social and interpersonal support (small networksize, low exchange of instrumental and emotional support), personality characteristics (neuroticism, more external locus of control) and impaired cognitive functioning (Vink, Aartsen et al. 2008). Furthermore, some somatic drugs may evoke depressive symptoms, e.g. several antihypertensive drugs, corticosteroids and benzodiazepines (Dhondt, Derksen et al. 1999; Dhondt, Beekman et al. 2002).

Gender and late life depression

Considering the preponderance of women in depression and in older age, it is important to know if there are particular aspects of depression in older women that need specific attention. Besides, changes in mood-related hormones and in social roles and status in aging women may be related to changes in patterns of depressive problems, and may help to unravel facets of the etiological background of depression.

However, many gender aspects of late life depression are still unknown or findings are not conclusive. It is often stated that in older age the gender-gap diminishes or disappears

(Krause 1986; Jorm 1987; Bebbington, Dunn et al. 1998; Noble 2005), but there also is evidence that this is not the case (Beekman, Copeland et al. 1999; Prince, Beekman et al. 1999; Cairney and Wade 2002) so this issue still remains undecided. It is not clear if symptom profiles in late life depression are different for men and women, like in younger adults.

Considering the risk factors for depression in older age, interesting gender differences were found, in vulnerability as well as in exposure to these risk factors. Older women seem to be more vulnerable to develop depression than older men when they experience long-lasting financial problems such as debts, an increasing number of life events, and have low social contact and attachment, particularly when they are living alone (Krause 1986; Husaini, Moore et al. 1991). Furthermore, older women are found to be more sensitive to life events that occur to other persons than men (Kessler, Price et al. 1985) (Maciejewski, Prigerson et al. 2001). On the other hand, older men are more vulnerable for depression when they lose their partner, have a low income or receive little emotional support (Beekman, Deeg et al. 1995; van Grootheest, Beekman et al. 1999). Next to vulnerability, also the exposure to risk factors for late life depression is different in men and women. Older women experience more disabling chronic diseases, they lose more often their partner and they have lower education and income than older men (Beekman, Deeg et al. 1995).

In later life, the relationship between depression, gender and social support is even more complicated. In general, older persons with a partner are less depressed than people without a partner. However, when there is a partner with physical or mental health problems, women are more depressed than men. In older married couples that have to cope with functional diseases, the presence of functional impairment leads to lower well being in both men and women (Korporaal, Broese van Groenou et al. 2008). However, the presence of social support in these couples leads to better well being only in men (Robb, Small et al. 2008). It seems that older men profit of social support, received and given, as buffer against depression, and older women do not (Takizawa, Kondo et al. 2006). Gender differences in feelings of responsibility and obligation towards the partner are postulated to explain the different effect of support for men and women, leading to more stress in women in these situations, but studies on this subject are scarce.

Treatment in late life depression

Without treatment, depression in older people shows an unfavourable natural course. In the community, a pattern of waxing and waning of depressive symptoms in more than half of the depressed group has been found (Beekman, Geerlings et al. 2002). Biological treatment and psychotherapy appear to be effective in older people (Hinrichsen 1992; Reynolds 1994; Reynolds, Frank et al. 1994; Schneider and Olin 1995; Reynolds, Frank et al. 1996; Reynolds, Frank et al. 1996; Little, Reynolds et al. 1998; Miller, Cornes et al. 2001; Cuijpers, van Straten et al. 2006; Pinquart, Duberstein et al. 2006). However, several studies show undertreatment, also in older people with severe depressive symptoms (Copeland, Davidson et al. 1992; Cole, Bellavance et al. 1999; Streim, Oslin et al. 2000; Stek, Gussekloo et al. 2004). This undertreatment may be due to difficulties in diagnosing depression in older people (Van Exel, Stek et al. 2000; Stek, Vinkers et al. 2006). As is already mentioned above, depression in older people often does not fulfil the complete DSM-criteria for Major Depressive Disorder, but nevertheless is considered to be of clinical relevance and in need of treatment. Next, clinical presentation of depressive symptoms in older people has been thought to be different from younger adults, with a more somatic presentation and loss of interest instead of depressed affect and negative thoughts. Although sometimes this pattern is found, results on this topic are inconclusive (Newmann, Engel et al. 1990; Hybels, Landerman et al. 2012). Often a combination is found of clear depressive symptomatology with other problems, such as somatic complaints, anxiety and behavioural changes, which seems to make the diagnosis of a depressive syndrome or disorder more complicated. A comorbid somatic illness may complicate the diagnostic process, particularly when symptoms are similar such as psychomotor slowing and problems with getting started in Parkinson's disease. Sometimes hesitation to give medical treatment to persons with somatic or cognitive comorbidity or with other pharmacotherapeutic drugs may play a role (Kennedy and Marcus 2005).

Antidepressant medication has the same effectiveness in older as in younger depressed adults (Wilson, Mottram et al. 2001; Mottram, Wilson et al. 2006). However, in older people antidepressant medication is often not prescribed at all, or in low, non-therapeutic dosages, and often discontinuation of the medication is performed too early (Cole, Bellavance et al. 1999; Streim, Oslin et al. 2000). Psychotherapeutic interventions such as interpersonal psychotherapy and cognitive behaviour therapy have shown to be effective, but they are not regularly offered to older patients (Miller, Cornes et al. 2001). ECT has found to be

very effective in severe depression in older people, particularly in depression with psychotic symptoms and psychomotor disturbances (Stek, van der Wurff et al. 2007; O'Connor, Lebowitz et al. 2008).

In the last twenty years, new antidepressants such as the SSRI's, SNRI's and the atypical antidepressants have become available, and they are considered to be suitable for applying in depression in older people. These new antidepressant drugs are more easily to apply than TCA's, due to more simple dosing schemes and less cardiovascular side effects, which is often a problem in older people. It is not clear if these new antidepressants have improved the rate and the results of treatment of depression in older people, or that the diagnostic problems or doubt about the effectiveness of the therapies still predominate.

The Longitudinal Aging Study Amsterdam

The research was conducted within the Longitudinal Aging Study Amsterdam (LASA).

LASA is an ongoing study on determinants, trajectories and consequences of physical, cognitive, emotional and social functioning in the aging population in the Netherlands (Deeg and Westendorp-de Seriere 1994; Huisman, Poppelaars et al. 2011). The LASA study focuses on the changes in these four domains, the predictors of these changes and the consequences for autonomy, well-being and the need for care.

The LASA study started in 1991 and was initiated by the Dutch Ministry of Welfare, Health and Culture with the aim to investigate the expected need for health care in the near future for the rapidly growing rate of older people in the population, which was due to an increased number of births after World War II in combination with the rising life expectancy.

The LASA cohort is based on a nationally representative random sample of older adults between the ages of 55 and 85 years old, from three geographic regions in the Netherlands, that were chosen to provide an optimal representation of religious diversity and urban as well as rural areas. Each area consists of one middle- to large-size city and two or more rural municipalities which border on the city. The 11 municipalities included in the sample are: Amsterdam, Wormerland, Waterland (West), Zwolle, Ommen, Genemuiden, Zwartsluis, Hasselt (North-East), and Oss, Uden, Boekel (South).

The sample was drawn from the population registers of these municipalities, using a stratification procedure for age and sex. Older persons and particularly older males were

oversampled with the purpose of compensating the expected mortality five years into the study. The initial response rate, for another study on living arrangements and social networks (LSN) was 60% (n = 3805). 11 months after the LSN interview, the participants were approached to participate in the first LASA cycle. Response rate for this first LASA cycle was 85% (n = 3107). Every three years a measurement cycle was performed, thus leading up to six cycles until now. In 2002, 10 years after the first LASA cycle, an additional cohort was recruited, which made it possible to study cohort differences in the four LASA domains. Response rate was 55% (n = 1002). In the next LASA cycles, this second cohort was added to the first cohort, and followed the interview cycles of the first cohort.

The measurements were performed by trained interviewers who visited respondents at home. The main interview lasted about two hours, and was tape-recorded. Next to this interview, respondents were asked to fill out a written questionnaire which was given to them after the main interview. Information was gathered on demographics (sex, age, marital status, living situation, family, education, income, working career, religion etc.) and on the specific domains of the study (life style factors, chronic diseases, functional limitations, medication use, cognitive functions, anxiety, depression, live events, personality traits, quality of life, personal network, relationships with children, loneliness, social participation). After the main interview, respondents were asked to participate in a subsequent medical interview, which was performed in a separate visit. This medical interview consisted of additional questions and clinical measurements, e.g. blood tests and psychiatric diagnostics.

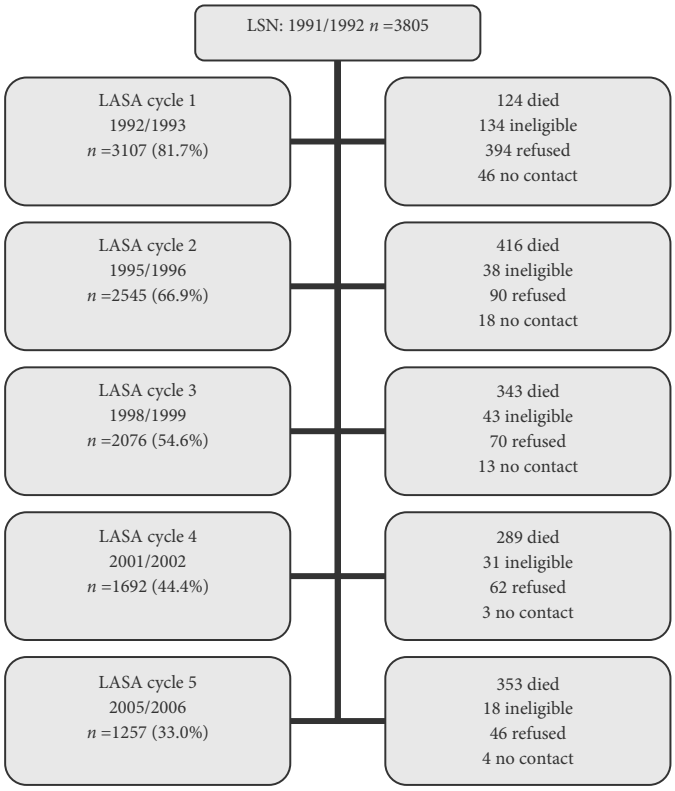
Attrition in LASA was mainly due to mortality, as could be expected in a longitudinal study in an aging population. Other reasons for attrition were refusal, being too frail or impossibility to contact. Attrition was associated with some of the predictors and outcome measures: level of education, chronic diseases and cognitive impairment.

Figure 1 shows the geographic distribution of the LASA sample.
Figure 2 shows the number of respondents in each LASA cycle, in both the first and the second cohort, with attrition numbers.

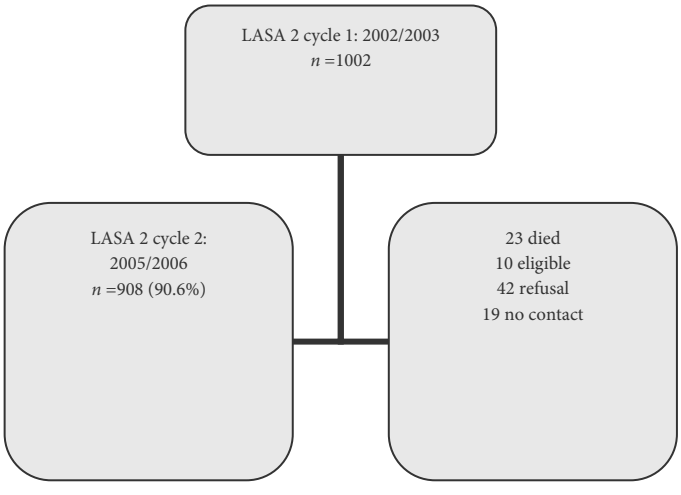
Figure 1. Geographic distribution of the LASA sample

Figure 2. Participation and attrition in the LASA study

2a. First cohort



2b. Second cohort



General aim of this thesis

The objective of the present thesis is to study sex differences and pharmacological treatment in late-life depression. The principle aims were to study:

I a the sex differences in prevalence, symptom profiles and risk factors in late life depression

I b the relation between sex, late life depression, religious denomination and social support

II a the use of antidepressants and benzodiazepines in late life depression

II b changes over time in the use of antidepressants and benzodiazepines in late life depression

Contents of this thesis

In the first part of the thesis, chapters 2-4, sex differences in late life depression are investigated. Chapter 2 focuses on sex differences in prevalence and symptom profiles, and in the vulnerability and exposure to risk factors for late life depression in the first LASA cycle. In chapter 3 sex differences in the relation between religious denomination and depression is investigated. In chapter 4 the relation between sex, depression and social support is assessed, and we test the hypothesis that sex differences in the perceived importance of social support, or need for social affiliation, play a role in the association between social support and depression in late life.

In the second part of the thesis, chapters 5-7, pharmacological treatment of late life depression is the central theme. In chapter 5, the use of antidepressants and benzodiazepines in the first LASA cycle is investigated, with assessment of predictors for non-treatment. Chapter 6 and chapter 7 focus on time trends of medication use. In chapter 6 trends in antidepressant use from 1992 – 2002 are investigated in the first LASA-cohort, testing our hypothesis that antidepressant use would show an increase, comparable to the time trends in younger adults. In chapter 7 trends in benzodiazepine use over 10 years are investigated, comparing the first with the second LASA cohort. We expect a decrease of benzodiazepine use over time, due to the changing guidelines on benzodiazepine use and on treatment of depression and anxiety.

Chapter 8 presents a brief summary of our findings, comments on their relevance, and a discussion on the strengths and the limitations of the study.

Table 1. Diagnoses of Major Depressive Disorder, Dysthymic Disorder and Minor Depressive Disorder (DSM-IV-TR, APA 2000)

Diagnostic criteria for Major Depressive Disorder (MDD):

A. Five (or more) of the following symptoms have been present nearly every day during the last 2-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure:
   1. Depressed mood most of the day, as indicated by either subjective report (e.g. feels sad or empty) or observation made by others (e.g. appears tearful);
   2. Markedly diminished interest or pleasure in all, or almost all, activities, most of the day (as indicated by either subjective account or observation made by others);
   3. Significant weight loss without dieting or weight gain, or decrease or increase in appetite;
   4. Insomnia or hypersomnia;
   5. Psychomotor agitation or retardation;
   6. Fatigue or loss of energy;
   7. Feelings of worthlessness or excessive or inappropriate guilt (may be delusional);
   8. Diminished ability to think or concentrate, or indecisiveness;
   9. Recurrent thoughts of death, recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.

B. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning

C. The symptoms are not due to a general medical condition, the use of a substance or bereavement

D. The symptoms are not better accounted for by or superimposed on a psychotic disorder

Diagnostic criteria for Dysthymic Disorder

A. Depressed mood for most of the day, for more days than not for at least 2 years

B. Presence, while depressed, of two or more of the following symptoms:
   a. Poor appetite or overeating
   b. Insomnia or hypersomnia
   c. Low energy or fatigue
   d. Low self-esteem
   e. Poor concentration of difficulty in making decisions
   f. Feelings of hopelessness

C. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning

D. The symptoms are not due to the direct physiological effects of a substance or general medical condition

E. The disturbance does not occur exclusively during the course of a psychotic disorder, or at any time has fulfilled the criteria of another mood disorder

Research criteria for Minor Depressive Disorder

A. A mood disturbance, defined as follows:
   a. At least two (but less than five) of the nine symptoms mentioned for the Major Depressive Disorder have been present during the same 2-week period and represent a change from previous functioning; at lest one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure
   b. The symptoms cause clinically significant distress or impairment in social, occupational, or other areas of functioning
   c. The symptoms are not due to the direct physiological effects of a substance or a general medical condition
B. There has never been a Major Depressive Episode, and criteria are not met for Dysthymic Disorder or better accounted for by bereavement
C. There has never been another mood disorder and criteria are not met for a psychotic disorder

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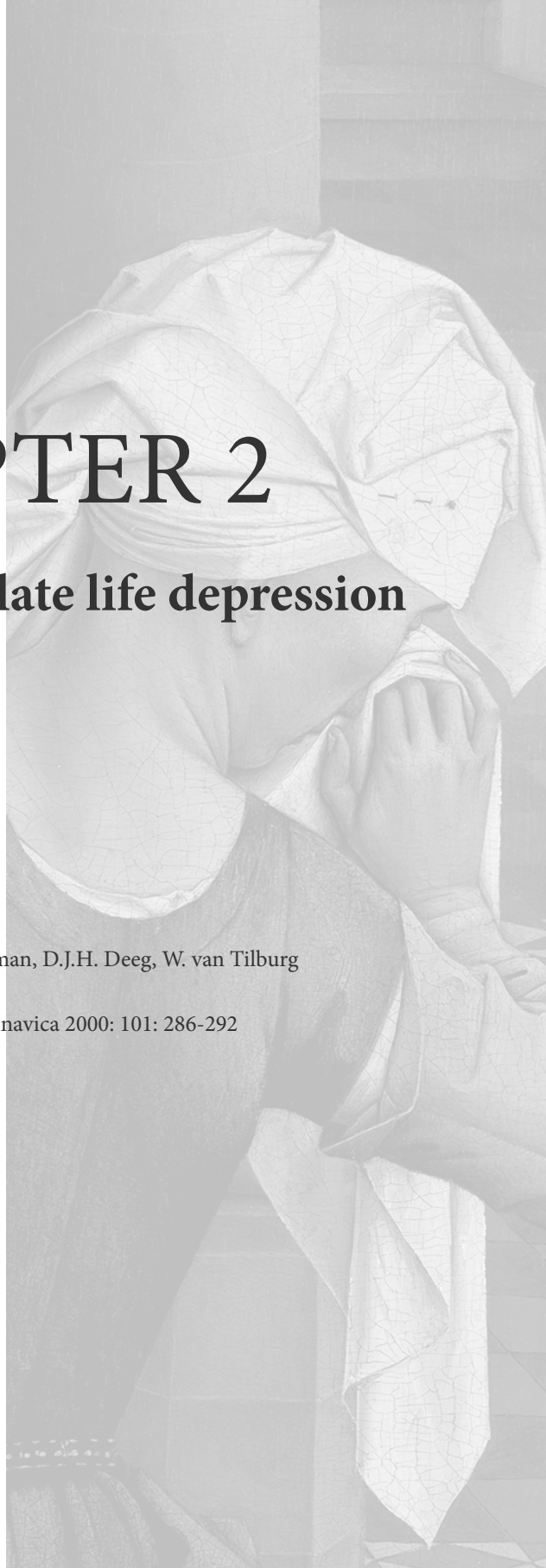

CHAPTER 2

Sex differences in late life depression

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Acta Psychiatrica Scandinavica 2000: 101: 286-292

ABSTRACT

Objective

The primary aim of this study was to assess sex differences in depression in later life.

Method

In a random, age and sex-stratified community sample of 3056 older Dutch people (55-85 years) the prevalence, symptom reporting and risk factors associated with depression in later life were studied. Depression was measured with the Center for Epidemiologic Studies Depression scale (CES-D). Bivariate, multivariate and factor analyses were used.

Results

Prevalence of depression in women was almost twice as high as in men. Controlling for age and competing risk factors reduced the relative risk for females with more than half. Symptom patterns in men and women were very much alike. Sex differences in associations with risk factors were small, but exposure to these risk factors was considerably higher in females.

Conclusion

*V*ery little evidence for a typical 'female depression' was found. Female preponderance in depression was related to a greater exposure to risk factors.

INTRODUCTION

In most clinical and community studies the prevalence of depression is higher in women than in men. In 1977 Weissman and Klerman reviewed this evidence in various types of studies conducted in the preview 40 years, including community surveys. Differential prevalence rates of depression for men and women varied from 1:1.5 to 1:3 (Weissman and Klerman 1977).

In the subsequent 20 years several clinical and epidemiological studies, both cross-sectional and longitudinal, were conducted on sex differences in depression (Angst and Dobler-Mikola 1984; Weissman, Leaf et al. 1984; Cross-National_Collaborative_Group 1992; Kessler, McGonagle et al. 1993; Weissman, Bland et al. 1993; Wilhelm, Parker et al. 1997). Generally, female preponderance in depression rates appears to be a consistent finding. The sex difference seems to be age-specific with little difference in childhood, a considerable difference in midlife (due to a sharp rise of depression in females) and a slight decrease of the difference in older age (Krause 1986; Jorm 1987).

In the literature a large number of possible explanations has been suggested and investigated, such as biological factors (endocrine), social factors (social roles and status, life events, social support), psychological factors (coping style) and the possibility of the difference being artefactual (sex differences in help seeking behaviour and/or symptom reporting, diagnostic bias) (Wolk and Weissman 1995) . In the elderly, chronic life strain (especially financial matters), increasing number of life events and low social contact and attachment, particularly in those living alone, seem to increase the risk of depression for women (Krause 1986; Husaini, Moore et al. 1991).

Newman et al. found two different types of syndromes in depressive older women: a 'classical' depressive syndrome (more classical form with negative affect, feelings of guilt), decreasing with age, and a so-called 'depletion' syndrome (marked by feelings of denervation and loss of interest), increasing with age (Newmann, Engel et al. 1990). This changing of symptom pattern may impede correct diagnosis in women. Because this phenomenon has not been studied in older men it is unclear what role it plays in diagnosing depression in older men and women.

The principal aim of the present study was to investigate sex differences in depression across older age. Most community based studies include low numbers of older males. Our sample

is stratified for age and sex, which allows comparison of depression in men and women throughout later life. The following questions were addressed:

1. Are there sex differences in the prevalence of depression in the elderly?
2. If so, can this be attributed to sex differences in symptom reporting, thus pointing towards an artefactual sex difference in prevalence, or to different types of depressive syndromes?
3. Are there sex differences in (a) the vulnerability and (b) the exposure to risk factors of depression, which may explain the sex difference in prevalence?

MATERIAL AND METHODS

Sample and procedures

Data were derived from the Longitudinal Aging Study Amsterdam (LASA), a 10-year interdisciplinary study on the predictors and consequences of changes in autonomy and well being in the aging population (Deeg and Westendorp-de Seriere 1994). Sampling procedures and characteristics of the sample have been described in detail in previous publications (Beekman, Deeg et al. 1995). In short, the LASA cohort is based on a representative random sample of older adults between the ages of 55 and 85, stratified for age, sex and expected mortality five years into the study. It was drawn from the population registers of 11 municipalities in three regions of the Netherlands, and was also used in another study prior tot LASA (NESTOR-LSN, *n*=6108, response rate 62.3%; non-response associated with age, sex and urbanicity). Of the 3805 LSN- participants, 3107 participated in LASA (response rate 81.7%; refusal rate 10.4%; deceased/too frail 6.8%; ineligible 1.2%). Non-response was related to age (partly due to illness or cognitive impairment), but not to sex. Due to item non-response (more than two missing items on the CES-D) 51 participants were lost, leaving a baseline sample of 3056.

Measurements

Depression was measured with the Center for epidemiologic Studies Depression scale (CES-D), a 20-item self-report scale developed for use in the community (Radloff 1977; Radloff, Teri 1985). Respondents scoring 16 or higher on this scale are considered to have a clinically relevant depressive syndrome. The CES-D has also proved to have good psychometric properties in elderly community samples in the Dutch translation (Beekman, van Limbeek et al. 1994), with a minimal overlap with physical illness (Berkman, Berkman

et al. 1986) and very good criterion validity for major depression (Beekman, Deeg et al. 1997).

Within the CES-D four valid factors or subscales are distinguished (Radloff 1977), also in the Dutch version (Van den Eeden, Smit et al. 1995): depressed affect (having the blues, feeling depressed, life a failure, feeling fearful, feeling lonely, crying, feeling sad), positive affect (feeling as good as others, hopeful about the future, being happy, enjoying life), somatic complaints and inhibition (being bothered, low appetite, trouble with concentration, everything an effort, restless sleep, talking less, cannot get going) and interpersonal problems (people unfriendly, people dislike me).

Building on previous findings ((Beekman, Deeg et al. 1995; Beekman, Deeg et al. 1997) the following risk factors of depression were studied: age, marital status, socioeconomic status (level of education attained and income), urbanicity, physical health (chronical illness (CBS 1989) and functional limitations (Van Sonsbeek 1988)), social and interpersonal support (size of personal network; exchange of instrumental and emotional support with network members Van Tilburg, Dijkstra et al 1992)), personality (locus of control) (Pearlin and Schooler 1978) and cognitive functioning (MMSE) (Folstein, Folstein et al 1975)).

Data analyses

Prevalence of depression in males and females in six age groups was calculated. Associations with sex were assessed in bivariate analyses, using odds ratios with 95% confidence intervals. Association between sex ratio and age was assessed by testing their interaction using logistic regression. To examine sensitivity of the sex difference to the threshold of the cut-off score of 16 used in the CES-D, analyses were repeated with thresholds of 12 and 20. Multivariate analyses were assessed to control for confounding, using logistic regression with depression as the dependent variable and sex, age and risk factors as independent variables.

Sex differences in symptom reporting were assessed in four ways. Mokken's scale analyses was used to assess sex differences in item response functioning or item difficulty (i.e. differences in the way men and women answer the questions of the CES-D). Sex differences in symptom patterns were assessed in factor analysis of the CES-D item scores in the full sample and in the depressive subsample, with separate analyses in men and women. We used principal components analysis with varimax rotation. Mean scores of the four subscales of the CES-D in men and women were compared using *t*-tests. To investigate sex differences in the separate item scores chi-square tests were used.

Sex differences in the vulnerability to risk factors were tested in bivariate associations by calculating odds ratios and 95% confidence intervals, in both sexes, for the separate risk factors. All odds ratios were calculated relative to the non-depressed group. Logistic regression was used with depression as the dependent variable, and age and the risk factors as independent variables.

Finally, sex differences in the exposure to these risk factors were examined. Differences in exposure to the risk factors in males and females, in the full sample as well as in the depressed subsample, were assessed by chi-square tests.

RESULTS

Description of the sample

In table 1, demographic and health-related characteristics of the sample are shown. The relatively high number of subjects unmarried, with cognitive impairment of physical health problems, is due to oversampling among the older old. Due to higher non-response among the older old and the very frail, subjects in institutions are under-represented.

Sex differences in the prevalence of depression

Table 2 shows prevalence rates in the six age groups in the full sample, in males and in females and the sex ratio. Prevalence rates in the full sample and in females were found to be lowest in the youngest age group, rising gradually with age. In males, rates appeared to fall until the age of 70, after which they increased, but not to the same extent as in females. Prevalence of depression was previously described by Beekman et al (Beekman, Deeg et al. 1995). Considering the sex ratio, in the full sample the odds ratio for females compared to males was 1.78. In the youngest age group there was no significant sex difference. In the other age groups prevalence in women was significantly higher than in men. Testing for interaction effects between sex ratio and age showed a non-linear, third power association (B=0.02; SE= 0.0048; $P<0.001$). Repeated analyses with CES-D thresholds of 12 and 20 yielded similar results (analyses not shown).

In the multivariate analyses the relative risk for females was reduced from RR=1.78 (CI=1.58-1.99) to RR=1.33 (CI=1.04-1.61) but remained significant. Therefore, confounding by age and competing risk factors existed, but only partially explained the effect of sex on depression.

Table 1. Characteristics of the sample

Variables		**N**	**%**
Age (years)	55-59	458	15.0
	60-64	506	16.6
	65-69	494	16.2
	70-74	460	15.1
	75-79	570	18.7
	80-85	568	18.6
Sex	Male	1478	48.4
	Female	1578	51.6
Marital status	Married	1920	62.8
	Not married	1136	37.2
Level of education	Low	1340	43.8
	Middle / high	1711	56.0
Income in Dutch fl.	<2000 per month	1155	44.7
	2000 pm or more	1427	55.3
Living in a big city	Yes	847	27.7
	No	2209	72.3
Living arrangement	Independent	2946	96.4
	Old age residence	93	3.0
	Nursing home /hospital	17	0.6
Depressive symptoms	CES-D <16	2602	85.1
	CES-D > 15	454	14.9
Cognitive functioning	MMSE <24	2567	84.0
	MMSE 24-30	473	15.5
Chronic physical illness	None	1026	33.6
	One or more	2030	66.2
Physical limitations	None	1787	58.5
	One or more	1239	40.5

Table 2. Prevalence of depression by age and sex, odds ratios (sex ratio) and confidence intervals

Age	% Depressed	% Depressed males	% Depressed females	Odds ratio (relative risk for females)	95% CI
Full sample					
55-85	14.9	11.2	18.3	1.78	**1.45-2.19** *
Age groups					
55-59	10.7	12.1	9.1	0.71	0.39-1.28
60-64	11.5	7.3	15.5	2.34	**1.30-4.21** *
65-69	13.2	7.0	17.9	2.91	**1.59-5.34** *
70-74	14.3	10.6	18.0	1.86	**1.08-3.19** *
75-59	18.6	14.6	22.9	1.74	**1.13-2.67** *
80-85	19.4	13.8	24.7	2.05	**1.33-3.16** *

* = 95% confidence interval > 1 = significant

Sex differences in symptom patterns

Mokken's scale analyses of the CES-D scale showed almost similar item response functioning for men and women in the complete CES-D scale, and in three of the four subscales (depressed affect, positive affect and interpersonal problems) with reliable scalability coefficients (Loevinger's H weighted >0.30). Small sex differences were found in the somatic complaints/inhibition subscale: three items were similarly scaled for men and women, two items (being bothered and talking less) were not scalable for men and low for women (H=0.30), and two items (low appetite and restless sleep) were not scalable for both sexes (H<0.30). In general, item difficulty appeared to be similar for men and women.

Factor analyses of the twenty CES-D item scores also showed very few sex differences. Results are shown in table 3. For convenience of comparison the CES-D items are arranged according to the four original subscales of the CES-D. Factor loadings >0.40 were considered meaningful; lower leadings are in brackets. In the full sample factor loading according to the four original subscales of the CES-D was found for most items, with the pattern for women and men very much alike. Exceptions were the items 'feeling as good as other people', 'thinking life is a failure' and 'restless sleep', which had fairly weak loadings and loaded on different factors in males and females. In the depressed subsample similar patterns were found (results not shown).

Table 3. Factor loading of the CES-D itemscores

	CES-D subscale							
	Negative affect		Positive affect		Inhibition		Interpersonal	
	Male	Female	Male	Female	Male	Female	Male	Female
Having the blues	0.64	0.67						
Feeling depressed	0.64	0.57						
Life a failure	(0.32)	(0.29)			(0.35)			(0.36)
Feeling fearful	(0.38)	0.55						
Feeling lonely	0.60	0.50						
Crying	0.74	0.80						
Feeling sad	0.76	0.79						
Feeling good			(0.39)	0.45	0.54			
Hopeful about future			0.68	0.72				
Being happy			0.76	0.75				
Enjoying life			0.76	0.72				
Being bothered	0.49	0.54			(0.18)	(0.30)		
Low appetite					0.51	0.61		
Trouble concentrating					(0.38)	0.47		
Everything an effort					0.63	0.72		
Restless sleep	(0.31)				(0.29)	(0.38)		
Talking less					0.53	(0.36)		
Cannot get going					0.66	0.67		
People unfriendly							0.80	0.80
People dislike me							0.73	0.81

Mean scores on the four subscales in the full sample showed small but statistically significant sex differences for negative affect, positive affect an inhibition/somatic complaints; on the negative affect subscale and the inhibition subscale women scored only one point higher (range 0-21); on the positive affect subscale (range 0-12) 0.5 point higher. In the depressed subsample the same sex difference was found for negative affect and inhibition, but no difference for positive affect. No significant sex differences were found for the subscale 'interpersonal problems'.

At the symptom level, women scored significantly higher on almost every CES-D item, except for the interpersonal items and one inhibition item (talking less) on which scores were similar. In the depressed subsample this sex differences disappeared, except for the items 'crying' and 'feeling sad' (P<0.001) and 'disturbed sleep' (P<0.01), on which women scored significantly higher.

Sex differences in associations with and exposure to risk factors

Table 4 shows the results of the bivariate analyse. Significant sex differences are marked. Higher odds ratios for men than for women were found for not or no longer being married, low income and low emotional support received, indicating a stronger association between these risk factors and depression in men.

Table 4. Odds ratios and 95% confidence intervals in males and females for risk factors of depression

Independent variable	Males		Females	
	OR	CI	OR	CI
Marital status				
not/ no longer married	**3.09**	**2.22-4.32**	**2.10**	**1.61-2.74** *
Level of education				
low level	1.68	1.21-2.33	1.49	1.15-1.94
Income				
low (< dfl 2000/m)	**2.20**	**1.52-3.19**	**1.47**	**1.09-1.98** *
Urbanicity				
living in a big city	1.87	1.34-2.62	1.90	1.46-2.49
Chronic physical illness				
one or more	2.31	1.57-3.41	2.12	1.54-2.90
Physical limitations				
one or more	4.19	2.98-5.91	3.34	2.53-4.42
Cognitive impairment				
MMSE < 24	2.56	1.76-3.71	1.93	1.41-2.66
Network size				
small (< 50%)	1.97	1.38-2.84	1.74	1.33-2.29
Instrumental support received				
low (< 50%)	1.10	0.77-1.57	0.90	0.69-1.19
Emotional support received				
low (< 50%)	**1.96**	**1.34-2.86**	**1.21**	**0.92-1.59** *
External locus of control				
high (< 50%)	6.07	4.29-8.59	6.31	4.76-8.37

Printed in bold with * = significant difference between males and females (odds ratio outside confidence interval)

In the multivariate models independent sex differences in the associations with depression were found for not or no longer being married (males: OR=2.51, CI=1.69-3.91); females: OR=1.57, CI=1.07-2.29) and low emotional support received (males: OR=1.18, CI=0.73-1.90; females: OR=0.68, CI=0.47-0.99).

With regard to exposure to risk factors substantial sex differences were found. Results are shown in table 5. Women were exposed significantly more often to: not or no longer being married, having completed a lower level of education, having a lower income, having one or more chronic physical illnesses and having one or more functional limitations. Men received less emotional support.

Table 5. Sex differences in exposure to the risk factors

Risk factor	% Males	% Females
Marital status		
not/ no longer married	**24.4**	**49.2** *
Level of education		
low level	**32.9**	**54.2** *
Income		
low (< dfl 2000/m)	**32.1**	**57.3** *
Urbanicity		
living in a big city	28.3	27.2
Chronic physical illness		
one or more	**63.3**	**69.2** *
Physical limitations		
one or more	**34.5**	**47.0** *
Cognitive impairment		
MMSE < 24	15.6	15.5
Network size		
small (< 50%)	47.2	45.7
Instrumental support received		
low (< 50%)	47.5	47.4
Emotional support received		
low (< 50%)	**55.2**	**44.7** *
External locus of control		
high (< 50%)	59.6	64.0

Printed in bold with * = significant difference in exposure between males and females

DISCUSSION

The results confirmed the existence of sex differences in the prevalence of depression in the elderly, with older women appearing to be at a higher risk. The mean sex ratio in our study was 1.78, which corresponds to those found in studies of younger adults. Unlike in other studies (Krause 1986; Jorm 1987) the gender gap did not decrease or disappear with increasing age, but appeared to shift around the mean with an increase of the gap in the 60-70-year-olds, caused by a decrease of the prevalence in males in these age groups. Controlling for age and competing risk factors still showed female sex to be an independent, statistically significant risk factor for depression in the elderly.

Investigation of symptom reporting showed only minor sex differences in item difficulty. In the three levels of analyses, symptom patterns were very much alike, with women scoring slightly higher on almost every dimension and on almost every item of the CES-D. In the depressed subsample the same pattern was found. Significantly higher scores for women remained for three items, one of them being 'crying'. This may be a confirmation of the widely held assumption that men admit to crying les readily than women, also in the elderly. It can be concluded that, in general, women did not report different symptoms or symptom clusters than men. They reported more symptoms on the full range of the CES-D, which corresponds with the higher prevalence of depression in females.

The association of depression with risk factors was similar in men and women. Notable exceptions were: not or no longer being married, low income and low emotional support received, the data suggesting that men are more prone to depression in particular socio-economic circumstances. This fits with the findings of Krause (Krause 1986), that older women were not more vulnerable than men to the effect of network crises, and with the results of another study in LASA, with males being more vulnerable to depression following widowhood (van Grootheest, Beekman et al. 1999). A possible explanation can be found in the theory of Gutman (Gutmann 1976), who hypothesized that there may be a reversal of emotional roles in late midlife: women tend to be more assertive, and men tend to be more concerned with the emotional and nurturing aspects of life than they used to be earlier in life.

So far, little evidence has been found to explain the female preponderance in the prevalence of depression. On the contrary, males appeared to be slightly more vulnerable to some of the risk factors.

However, the effect of the risk factors changed when sex differences in exposure to these risk factors were taken into account. This absolute risk appeared to be of much more importance than the relative risk (or vulnerability), and explained part of the female preponderance in depression.

Limitations

An important limitation of the present study is the use of self-report scales. Sex differences in reporting depressive symptoms may lead to report bias and/or diagnostic bias. Angst et al. (Angst and Dobler-Mikola 1984) and Ernst et al. (Ernst and Angst 1992) found that men reported fewer depressive symptoms than women at the same degree of impairment of psychosocial functioning, thereby possibly causing an artefactual female preponderance in depression. However, other studies failed to confirm this observation (Wolk and Weissman 1995). A second problem of the CES-D is that no information is given on depressive episodes and life events in the past; they are known to be important for developing depression later in life.

Another possible source of report bias is that depressed subjects may report more negatively about their mental and physical health status and about their social support and network. If the degree to which this occurs is different for men and women, this could influence the sex differences in the associations with the risk factors. A fourth potential source of bias is non-response, with non-responders being older, more often female and more often in poor health. Because the sample is stratified for age and sex, and risk factors for depression were well represented in men and women throughout the age strata, the sample is suitable for comparing prevalence data, symptoms and relative risks, which was the purpose of the present paper. However, bias due to non-response cannot be ruled out, limiting the generalizability of the results, especially to the older-old and very frail.

The fifth limitation is the data being cross-sectional, which makes it impossible to draw definite conclusions about causal relationships between variables, such as partner loss, losing income or changing level of emotional support.

Conclusions

The present study confirms the existence of female preponderance in depression, also in the older old. Controlling for age and other risk factors reduces the relative risk for depression for females considerably, but it remains significantly higher than for males. This female

preponderance is not caused by sex differences in symptom reporting. Considering risk factors for depression, sex differences in exposure to several risk factors appear to be more important than the slight and reverse sex differences in vulnerability to some of these factors.

Thus, a typical 'female depression' with a specific symptom profile or specific factor profile has not been found, at lest not in the elderly. What is different in men and women is their level of exposure to negative socio-economic circumstances.

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CHAPTER 3

Religious denomination as a symptom-formation factor of depression in older Dutch citizens

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International Journal of Geriatric Psychiatry 2000: 15: 458-466

ABSTRACT

Objectives

The type of symptoms in depression is likely to be influenced by cultural environment. As religion represents an important cultural resource for older adults, it is hypothesized that religious denomination represents a symptom-formation factor of depression in the older generation. Focusing on older Dutch citizens, it is expected that depressed Calvinists report (1) less depressed affect, (2) more vegetative symptoms, and (3) more guilt feelings than Roman Catholics and non-church members.

Methods and procedures

The Center for Epidemiologic Studies Depression Scale (CES-D) was used to distinguish depressed (*N*=395) and non-depressed (*N*=2333) older adults, and to assess depressive symptom-profiles. The Diagnostic Interview Schedule (DIS) was used to assess major depressive episodes and criterion-symptoms of depression.

Results

Depressed Calvinists, especially the males, had higher scores on the vegetative CES-D subscale. Among those who have had a major depressive episode in later life (*N*=84), support was found for all hypotheses. Feelings of guilt were also more prevalent among Roman Catholics.

Conclusions

Religious denomination modified the type of symptoms in late-life depression. As a Calvinist background was associated with less depressive affect and more inhibition, there is a risk of underdiagnosis of major depression in older Calvinists in the Netherlands.

INTRODUCTION

In their work on the social origins of depression, Brown and Harris (Brown and Harris 1978) distinguish provoking agents, vulnerability factors and protective factors. In addition, they discern symptom-formation factors, which influence the expression of, or the type of depressive symptoms, regardless whether they are related to the etiology of depression. Identification of symptom-formation factors may help to understand the effects of socio-cultural determinants of depression. Nevertheless, they have received little attention in empirical research. As many older adults have moved through important phases of the life-cycle within the context of a particular religious tradition, this tradition may act as either a vulnerability factor or a protective factor. Evidence for these possibilities has been provided by previous studies (Kennedy, Kelman et al. 1996; Braam, Beekman et al. 1998; Braam, Beekman et al. 1999). The objective of the present study is to evaluate religious tradition as a possible symptom-formation factor.

Comparisons of older to younger depressed people have lead to the suggestion that affective symptoms and feelings of guilt become less prevalent with age, whereas somatic symptoms become more pronounced (Blazer 1982; Newmann, Engel et al. 1991; Koenig and Blazer 1992; Blazer, Kessler et al. 1994). Irrespective of age, culture also appears to influence the expression of depression (Weiss and Kleinman 1988). For example, there is evidence that the Christian heritage favours the expression of feelings of guilt, whereas symptoms of somatization are more prevalent in non-Western cultures or minorities (Murphy, Wittkower et al. 1964; Murphy 1982; Sartorius, Davidian et al. 1983; Ball and Clare 1990; Ulusahin, Basoglu et al. 1994; Tanaka-Matsumi and Draguns 1996).

The religious climate in the Netherlands is based on Calvinist, Roman Catholic, and secularized traditions. How Calvinism influences social and moral life has been thoroughly described by the sociologist Max Weber (Weber 1904). Weber concludes that the Calvinist way of life enhances rationalism, individualism, ascetism, and the systematic avoidance of expressing impulses and feelings. The relationship between the Calvinist individual and God has been suggested to be guilt-ridden (Murphy 1982). The Calvinist 'de-enchantment of the world' contrasts with the dualistic Roman Catholic attitude: a saintly minority (e.g. in monasteries and convents) adheres to an ideal of ascetism, but the majority of people accept the enjoyment of life in the present world. Thus, most Roman Catholics would express impulses and feelings in a similar way as non religious persons, and suffer less guilt feelings than Calvinists.

In the present study, two hypotheses are addressed:

1. Religious denomination acts as a symptom-formation factor of depression in later life. Symptom-formation of depression can be distinguished from normal expression of emotions by comparing the depressed with the non-depressed. A symptom-formation effect is only expected to be found in the depressed.
2. Depressed Calvinists report
    a. less affective symptoms of depression, but
    b. more feelings of guilt,
    c. and more vegetative (sleep or appetite problems) or cognitive (feeling inhibited, loss of concentration) symptoms, compared to Roman Catholics and non-church members.

The hypotheses are examined in a community-based sample of older Dutch citizens. As is discussed by Wolk and Weissman (Wolk and Weissman 1995), the symptom pattern of depression may be influenced by gender differences. The results are therefore, where possible, specified by gender.

MATERIAL AND METHODS

Sample and procedures

The present study is part of the Longitudinal Aging Study Amsterdam (LASA), a 10-year interdisciplinary study on predictors and consequences of changes in autonomy in the aging population (Deeg and Westendorp de Serière 1994). Most details on sampling and response have been described in previous publications (Beekman, Deeg et al. 1995; Braam, Beekman et al. 1998). The cohort is based on a random community sample, stratified for age and sex, based on registries of 11 municipalities in areas in the West (most secularized), North-East (predominantly Calvinist), and South (Roman Catholic) of the Netherlands. A characteristic of this country is that rivalry between Calvinist (i.e. Reformed) Protestant, Roman Catholic, and secularized traditions dominated sociocultural life profoundly, especially in the generations which have grown up in the first half of this century (Peters and Schreuder 1987). The sample is based on an earlier study, 10 months prior to LASA, in which 3805 respondents participated (net response rate 62.3%). A total of 3107 respondents were willing to participate in the main LASA interview. Complete data were obtained from 2728 respondents. Compared with the original sample (N=3805), non-response was related

to age (t =9.7, p <0.001), non-responders being older, but non-response was not related to sex or church-membership.

To study the process of symptom-formation, the sample is divided into a depressed sub-sample (N=395) and a non-depressed sub-sample (N=2333), according to a depression screening procedure (see below). In addition, the Diagnostic Interview Schedule (DIS) (Robins, Helzer et al. 1981) was administered to the depressed sub-sample (response N=300), and to a control group of equal size (N=297), randomly selected from the non-depressed respondents (see Table 1). This was done in a second interview within approximately one month (mean lag-time 32.6 days, SD 24.4) after the main LASA assessment.

Table 1. Numbers of respondents with complete data in the LASA baseline sample, and in the DIS sub-sample, distinguished for respondents screened as depressed and non-depressed

	total	**sub-samples**
Prior study	3805	
LASA baseline interview:		
Total sample	3107	
Data complete	2728	
Depressed (CES-D ³16)		395(*)
Non-depressed (CES-D <16)		2333(*)
DIS administered	660	
Data complete	597	
Depressed (CES-D ³16)		300
Non-depressed (CES-D <16)		297
MDD, lifetime diagnosis	99	
Depressed (CES-D ³16)		82
Non-depressed (CES-D <16)		17
Last episode of MDD after age 55	84(*)	

(*) selected for present study

Instruments

Dependent variable.

Depressive symptoms were measured using the Center for Epidemiologic Studies Depression Scale (CES-D, Radloff 1977) and the Diagnostic Interview Schedule (DIS) (Robins, Helzer et al. 1981). The CES-D is a 20-item self-report scale developed to measure depressive symptoms in the community. Items are scored on a four-point scale (0-3), designating the

frequence of occurence in the last week. In most studies the cut-off for a *depressive syndrome* which is probably clinically relevant is 16 (Berkman, Berkman et al. 1986; Beekman, Deeg et al. 1997). This cut-off point was also applied to screen for depression at syndrome-case level in the present study.

Radloff distinguished four factors, or subscales, within the CES-D (Radloff 1977; Radloff and Teri 1986; Hertzog, Alstine et al. 1990; Idler and Kasl 1997)), which also emerged in the Dutch version (Van den Eeden, Smit et al. 1995). The subscales are: *negative affect* (having the blues, feeling depressed, life a failure, feeling fearful, lonely, crying, and feeling sad) (Cronbach α=.82); *positive affect* (feeling as good as other people, feeling hopeful about the future, being happy, and enjoying life) (α=.70); *inhibition and vegetative problems* (being bothered, loss of appetite, trouble keeping mind on, everything is an effort, restless sleep, talking less, and can't get going) (α=.70); finally, the *interpersonal problems* subscale consists of only two items (people unfriendly, people dislike me) and was not used as a dependent variable in the present study.

The depression section of the DIS (Robins, Helzer et al. 1981) was used to assess the criterion symptoms of major depression, according to a structured procedure developed for epidemiological studies. The present study included the questions on (1) depressed affect, (2) appetite and weight, (3) sleep, (4) tiredness, (5) inhibition, (6) agitation, (7) sexual interest, (8) worthlessness and guilt, (9) concentration, and (10) thoughts about death and suicide. Pondering death may have a different meaning for older adults than it has for younger adults for whom the classification was designed. Therefore, the item on thinking about death is examined separately from the items on suicidal ideation, intent, and previous suicide attempts (11).

The DIS allows diagnosing depressive episodes in different time frames (ongoing, past week, past month, past 6 months, past year, lifetime). The present study included all subjects who suffered an episode of major depressive disorder (MDD) after age 55. This had the advantage that a substantial number of subjects could be included in the analyses which pertained to major depression in later life (N =84).

Independent variable.
Religious denomination was categorized as Calvinist, Roman Catholic and 'no denomination'. Calvinists are members from the Dutch-Reformed church (*Nederlands Hervormd*),

the Reformed Calvinist churches (*Synodaal Gereformeerd*), and small, conservative Calvinist congregations. Other denominations were reported by 2% or less of the sample and were not included in the present study. Because subjects of the 'no denomination' group may have been exposed to religious ideas in early life, the religious denomination of the parents is subject of additional analyses. Three groups are distinguished: (1) both parents non-religious (N = 458), (2) at least one parent Calvinist (N = 284), and (3) at least one parent Roman Catholic (N = 196). The remainig groups, mixed denominations of the parents (N = 20), non-Calvinist protestants (N = 51) and denomination unknown (N = 54), were omitted.

Confounders.
Demographic characteristics were sex, age, marital status, and years of education. Because poor physical health may affect the way of reporting depressive symptoms in later life, two measures were included (Kriegsman, van Eijk et al. 1997). Functional limitations were assessed by asking respondents whether they experienced difficulties with (1) climbing stairs, (2) using own or public transport or (3) cutting own toenails (Van Sonsbeek 1988). Answering categories ranged from 0 'no difficulty' to 3 'unable' (range 0-9). In addition, self-reports were obtained for six chronic diseases that are most prevalent in the older population: chronic lung disease, cardiovascular disease, stroke, diabetes, cancer, and arthritis (CBS 1989).

Data analysis

Two approaches were chosen to test the hypotheses. The first approach involved the CES-D, the second the DIS. In both approaches, the distribution of depressive symptoms was compared for both Roman Catholics and Calvinists, relative to non-church members, who represented the reference group.

The first approach involved the comparison of mean scores on the three CES-D sub-scales, and was employed in the depressed sub-sample (CES-D score $^{3}16$; N = 395). The analyses were repeated for the non-depressed (N = 2333). Associations between the three CES-D subscales and the denominational categories were tested using multiple regression analysis, controlling for effects of demographic and physical health variables. To assess gender-specific effects of religious denomination, the interaction-terms of the denominational categories with gender were evaluated in additional analyses. The interaction-terms were formed by multiplying the centered (deviation from the mean) scores of both components,

to avoid multi-collinearity between the first-order terms and the product terms. When the interaction-term was significant, stratified analyses were performed for the male and female subgroups (Aikin and West 1991). Within the 'no denomination group', the religious denomination of the parents (Calvinist, Roman Catholic versus no exposure to religious ideas) is analysed in additional analyses.

The second approach focused on the DIS criterion-symptoms of depression, and was employed in the sample of those respondents who had an episode of MDD after age 55 according to the DIS ($N = 84$; see Table 1). Respondents with a last episode of MDD before age 55 ($N = 15$) were excluded. As has been shown by Beekman et al. (Beekman, Deeg et al. 1997), the sensitivity of the CES-D for a MDD with a recency of more than 1 year was rather poor. Therefore, diagnostic data from the non-depressed were also used, applying sampling probability weights to redress the effects of the two-stage screening procedure. The sample of those to whom a DIS was administered (CES-D < 16: $N = 297$, CES-D ³ 16: $N = 300$) was weighted to restore the original distribution of depressed and non-depressed subjects according to the CES-D criterion (CES-D < 16: $N = 2333$; CES-D ³ 16: $N = 395$). Associations between the DIS criterion symptoms of MDD and the denominational groups were analysed using logistic regression analyses, controlling for demographic and physical health variables.

RESULTS

Sample characteristics

As is summarized in Table 2, the three denominational traditions are well-represented in the sample. The Calvinists were somewhat less depressed. In the depressed sub-sample, there were relatively more female, older, less educated, and widowed subjects, as well as subjects with functional limitations. These correlates of depression have been described in more detail by Beekman et al. (Beekman, Deeg et al. 1995).

CES-D Subscale differences between denominations within the depressed cohort

As shown in Table 3, no significant associations were found between the denominational categories and either the negative or positive affect subscales within the depressed cohort. On the vegetative subscale, however, Calvinists had significantly higher scores than non-church members ($\beta = 0.13$; $p = 0.013$; $R^2_{\text{added}} = 0.023$).

Two significant interaction effects were found: between gender and Roman Catholic denomination for the negative affect subscale (β = -0.10; p = 0.033), and between gender and Calvinist denomination for the vegetative subscale (β = 0.12; p = 0.021). Therefore, stratified regression analyses were performed for these two subscales according to gender (Table 3, middle panel). For *female* depressed respondents, no significant associations were found between the denominational variables and either the negative affect or vegetative subscale.

Table 2. Sample characteristics for the depressed (*N*=395) and non-depressed (*N*=2333) sub-sample, including the weighted sample of those with a episode of MDD after age 55 (*N*=84)

	Depressed (CES-D ≥ 16) *N*=395	**Non-depressed (CES-D < 16)** *N*=2333	**Major depression after age 55** *N*=84
categorical variables	**%**	**%**	**%**
Roman Catholic	32	31	33
Calvinist	24	31	20
No denomination	44	38	47
Female	63	51	75
Not married	9	6	5
Married	43	67	59
Divorced	7	4	8
Widowed	41	23	28
continuous variables (range)	**mean (SD)**	**mean (SD)**	**mean (SD)**
Age (55-86)	72.2 (8.7)	70.0 (8.6)	67.6 (9.1)
Years of education (5-18)	8.2 (3.2)	8.9 (3.3)	9.8 (3.9)
Functional limitations (0-9)	2.9 (3.0)	1.1 (2.1)	1.4 (2.4)
Chronic diseases (0-5)	1.2 (1.1)	0.7 (0.9)	0.7 (1.1)
CES-D total score (0-54)	22.9 (7.1)	5.3 (4.2)	15.8 (12.2)
Negative affect subscale (0-21)	6.7 (4.0)	0.8 (1.4)	
Positive affect subscale (0-12)	4.4 (2.6)	9.5 (2.4)	
Vegetative subscale (0-21)	8.0 (3.5)	1.9 (2.0)	

Among *male* depressed respondents, Calvinists reported significantly more vegetative complaints compared to non-church members (β = 0.31; p < 0.001; R^2_{added} = 0.077), and to Roman Catholics (β = 0.26; p = 0.045; not in table). Male Roman Catholics and male Calvinists had lower scores on the negative affect subscale than non-church members, but these differences did not reach statistical significance.

Additional analyses were performed in the male depressed group between the denominational variables and the separate seven items included in the vegetative subscale (results not shown). The items in the vegetative subscale which were more often reported by Calvinists are: 'everything was an effort' ($\beta = 0.19$, $p = 0.019$); 'talked less' ($\beta = 0.27$, $p < 0.001$); 'could not get going' ($\beta = 0.28$, $p = 0.001$). These items broadly identify feelings of being inhibited.

Table 3. Associations between religious denomination and CES-D subscales; standardized regression-coefficients, adjusted for effects by demographic and physical health variables

	Calvinist (*)		**Roman Catholic** (*)	
	β	***(p)***	***β***	***(p)***
Depressed cohort				
Negative affect	-0.03	(0.538)	0.03	(0.527)
Positive affect	0.04	(0.513)	0.03	(0.621)
Vegetative symptoms	**0.13**	**(0.013)**	0.09	(0.089)
Female depressed (*N*=248)				
Negative affect	0.00	(0.990)	0.13	(0.075)
Vegetative symptoms	0.06	(0.411)	0.09	(0.224)
Male depressed (*N*=147)				
Negative affect	-0.08	(0.354)	-0.11	(0.230)
Vegetative symptoms	**0.31**	**(0.000)**	0.12	(0.147)
Non-depressed cohort				
Negative affect	-0.04	(0.084)	-0.02	(0.469)
Positive affect	**0.07**	**(0.001)**	**0.14**	**(0.000)**
Vegetative symptoms	**-0.09**	**(0.000)**	**-0.09**	**(0.000)**

(*) 'No denomination' is reference category

A final series of analyses in the depressed group was performed for the 'no denomination group'. Depressed non-church members with at least one Calvinist parent ($N = 39$) and non-church members with at least one Roman Catholic parent ($N = 35$), were compared to those with parents without religious denomination ($N = 69$). The results are shown in Table 4. As was found in the total depressed sample, depressed non-church members with Calvinist roots have significantly higher scores on the vegetative subscale, compared to those with parents without religious denomination ($\beta = 0.08$, $p = 0.032$).

CES-D Subscale differences within the non-depressed cohort

The associations with CES-D subscales in the non-depressed cohort were entirely different from those in the depressed (Table 3, lower panel). Both the non-depressed Roman Catholics and Calvinists reported significantly more positive affect ($R^2_{added} = 0.015$) and less vegetative symptoms ($R^2_{added} = 0.005$) than non-church members. The associations between denominational background and vegetative symptoms in the non-depressed respondents were in the opposite direction as was found in the depressed.

Table 4. Depressed subjects *without* current religious denomination: associations between religious denomination of the parents and CES-D subscales; standardized regression-coefficients, adjusted for effects by demographic and physical health variables

	Calvinist background (*)		**Roman Catholic background** (*)	
	β	***(p)***	***β***	***(p)***
Depressed cohort: 'no denomination' group				
Negative affect	0.06	(0.097)	0.00	(0.992)
Positive affect	0.00	(0.964)	0.06	(0.107)
Vegetative symptoms	**0.08**	**(0.032)**	-0.02	(0.964)

(*) 'Parents without denomination' is reference category

Table 5. Criterion symptoms of depression and religious denomination in older Dutch citizens; printed in bold are significant differences compared to non-church members in logistic regression analysis, controlled for demographics and physical health status

***N*=84** *	**Calvinists (*N*=17) vs non-church members (*N*=39) O.R. (95% C.I.) ****	**Roman Catholics (*N*=28) vs non-church members (*N*=39) O.R. (95% C.I.) ****
Depressed affect	**0.004 (<0.001-0.31)**	0.06 (0.001-3.07)
Appetite problems	5.56 (0.98-31.5)	2.34 (0.62-8.86)
Sleep problems	18.8 (0.75-470)	2.81 (0.32-24.5)
Tiredness	0.71 (0.12-4.24)	**0.11 (0.02-0.54)**
Inhibition	**7.05 (1.68-29.5)**	0.84 (0.18-3.82)
Agitation	1.50 (0.40-5.64)	0.56 (0.17-1.87)
Loss of sexual interest	0.94 (0.20-4.52)	1.78 (0.44-7.31)
Worthlessness / guilt	3.30 (0.80-13.6)	**4.03 (1.12-14.4)**
Concentration problems	0.47 (0.10-2.12)	0.89 (0.23-3.41)
Thoughts about death	6.10 (0.92-40.2)	2.05 (0.54-7.78)
Thoughts about suicide	0.57 (0.12-2.82)	1.26 (0.35-4.46)

* weighted sample of those with an episode of MDD after age 55

** Odds ratio (95% confidence interval)

Criterion based symptom differences in those with a diagnosis of MDD in later life

The distribution of criterion symptoms of depression derived from the diagnostic interview across the denominational groups is shown in Table 5. This part of the analysis pertained to respondents with a diagnosis of MDD after age 55 (*N*=84). *Calvinists* (*N*=17) reported significantly less depressed affect (OR = 0.004; 95% CI = < 0.001-0.31), and more symptoms of inhibition (OR = 7.05; 95% CI = 1.68-29.5) than non-church members (*N*=39). Furthermore, although *p*-values are between 0.05 and 0.10, Calvinists tended to report more loss of appetite. sleep problems, feelings of worthlessness and guilt, and thoughts about death than non-church members. That these differences did not reach the 0.05 significance level was probably due to the low number of Calvinists with MDD in later life in the study sample. *Roman Catholics* (*N* = 28) reported significantly less tiredness (OR = 0.11; 95% CI = 0.02-0.54), and more feelings of guilt (OR = 4.04; 95% CI = 1.12-14.4) compared to non-church members. The prevalence of the feelings of guilt was similar among Calvinists (69%) and Roman Catholics (65%), whereas it was considerably lower among non-church members (40%). Comparing males and females separately did not provide meaningful results due to very low numbers of older males with MDD in later life (*N* = 21).

DISCUSSION

The present study addresses the question whether religious denomination is a symptom-formation factor for late life depression. Support was found for the first hypothesis, that religious denomination influences the expression and type of depressive symptoms in depressed older adults. The symptom-formation effects of religious denomination were evident in the depressed sample only. Where evident among the non-depressed, associations between religious denomination and symptom profiles were even in the opposite direction of those found in the depressed. This observation is in line with the concept of symptom-formation of depression, which especially pertains to the type of depressive symptoms expressed in those who are ill, and does not merely represent the normal expression of emotions.

The second hypothesis contained three components: depressed Calvinists were expected to report less affective symptoms of depression, more feelings of guilt, and more vegetative and cognitive symptoms, compared to Roman Catholics and non-church members. This hypothesis was tested in the sample of respondents who were screened as depressed according to the CES-D, and in the subsample of respondents who had a diagnosis of major depressive

disorder in later life, based on the diagnostic interview schedule (DIS). Taken together, the results support all three components of the hypothesis. When depressed, Calvinists expressed less affective symptoms than Roman Catholics and non-church members. This finding was most clearly demonstrated by virtue of the findings based on the DIS. Indeed, depressed Calvinists reported more vegetative symptoms and especially more symptoms of inhibition. More detailed analyses showed that the findings about symptoms of inhibition pertain exclusively to the male depressed respondents. Furthermore, in depressed non-church members with Calvinist roots, the tendency to report more vegetative complaints and more symptoms of inhibition was still significantly present, suggesting that religion represents a life-long symptom-formation factor. The highest percentage of feelings of worthlessness and guilt was found among Calvinists.

This last finding about feelings of guilt parallels the one of an earlier study in the Netherlands by Saenger (Saenger 1968), who found that psychiatric outpatients in the Netherlands reported more feelings of guilt and psychomotor retardation, compared to American outpatients. He attributed this finding to the Calvinist climate in the Netherlands. Nevertheless, in the present study, feelings of worthlessness and guilt were also prevalent, and statistically more pronounced, among Roman Catholics, compared to non-church members.

Comments on the approaches used

Two different approaches were applied to test the hypotheses of the present study. The first approach focused on those respondents with a depressive syndrome according to a relatively mild CES-D criterion. Although this criterion is accepted for goals of epidemiological research, it has the disadvantage that it includes many respondents who were not depressed according to diagnostic criteria. An advantage, however, of this approach is that the CES-D measures a broad range of depressive symptoms currently present. The results of the second approach, based on a structured psychiatric interview, were more pronounced than those based on the screening procedure. Here, the disadvantage is that only lifetime recency data were available to obtain a group of subjects with episodes of major depression in later life, large enough to be studied. It should be mentioned that the application of the DIS in three community studies that contributed to the Epidemiologic Catchment Area (ECA) program yielded controversial findings (Robins, Helzer et al. 1984). In the ECA study, the lifetime prevalences of major depression were consistently lower for the oldest age group, compared to all younger age groups. Robins and colleagues discuss several explanations, such as disorder-associated mortality, difficulty in recall, and less willingness to report symptoms.

In the present study, the lifetime recency data were restricted to diagnoses of depression after age 55, which might reduce the disadvantages of the application of DIS lifetime diagnoses. One may conclude that the advantages and disadvantages of both approaches, CES-D subscales and DIS, are complementary to each other.

A limitation of the present study concerns the non-response in the oldest age cohort. Oversampling in the more vulnerable strata has resulted in a considerable number of elderly leaving the sample, because of physical and cognitive impairment. This attrition decreases the generalizability of the findings to the most frail elderly, in whom vegetative complaints probably have a different meaning. Nevertheless, attrition did not lead to a sample of 'healthy elderly', as one third of the non-depressed sample and two-thirds of the depressed sample reported serious physical health problems.

A final methodological issue concerns the categorization of religious denomination. It might be argued that culture in the Netherlands has been dominated by Calvinist ethics, and that one should not expect impressive differences between the main religious traditions. This problem may be solved by specifying levels of religious practice and types of orthodox views. This would, however, require a larger sample of older depressed people.

The 'self-blaming' type of depression in church members

Higher levels of feelings of guilt were found not only among Calvinists, but also among Roman Catholics. This last result was not anticipated, and suggests that a relationship between depression and guilt-feelings may depend on religiousness as such, and not on the particular religious tradition. The Calvinist tradition has a reputation in the Netherlands as enforcing feelings of responsibility and guilt. This view overlooks the fact that guilt is an important issue also in the Roman Catholic tradition. Guilt symptoms have been viewed as characterizing the classical, 'self-blaming' type of depressive psychosis (Arieti and Brody 1974). This type of depression is expected to be more prevalent in people who have been raised in a more traditional, 'inner-directed' society, emphasizing responsibility, duty, and guilt, as would fit with most major religious traditions. Among persons grown up in the more modern, 'other-directed' society, the 'self-blaming type' type of depression might be replaced by the 'claiming type' of depression, in which guilt feelings play a secondary or no role (Arieti and Brody 1974).

Depression, the depletion syndrome, and religious denomination

In the literature on depressive symptomatology in later life, a distinction is made between depression and the 'depletion syndrome'. In this depletion syndrome, depressed affect and excessive guilt are less prominent than a more quiet form of personal despair, marked by a loss of interest in one's self and one's world (Newmann, Engel et al. 1991). The results of the present study suggest that the manifestation of depression in Calvinists at least partly matches this 'depletion syndrome', whereas depressed Roman Catholics and non-church members express the symptoms which are more characteristic of depression. Among depressed Calvinists, the tendency to report symptoms of inhibition and vegetative problems instead of depressive affect may lead to underdiagnosis of depression in this group.

The results of the present study strongly suggest that plain information on a patient's religious background may be relevant for recognition and treatment of depression in later life. The investigation and discussion of religious and cultural aspects are increasingly recognized as being desirable for an adequate therapeutic relationship and compliance with treatment (Lu, Russell et al. 1995). Another application of the present findings is that one may help patients to understand how psychopathology undermines, through symptoms of guilt and inhibition, personal resources which were previously expected to provide hope or consolation. Psychiatrists are more and more expected to be aware of the role of religion and spirituality in the patient's experience. The present empirical findings may provide tools to discuss the subject and to interpret individual cases. The findings warrant research on effects of other aspects of the sociocultural background on depressive symptomatology, which may add to the understanding of broader, cross-cultural differences in the presentation of depression in later life.

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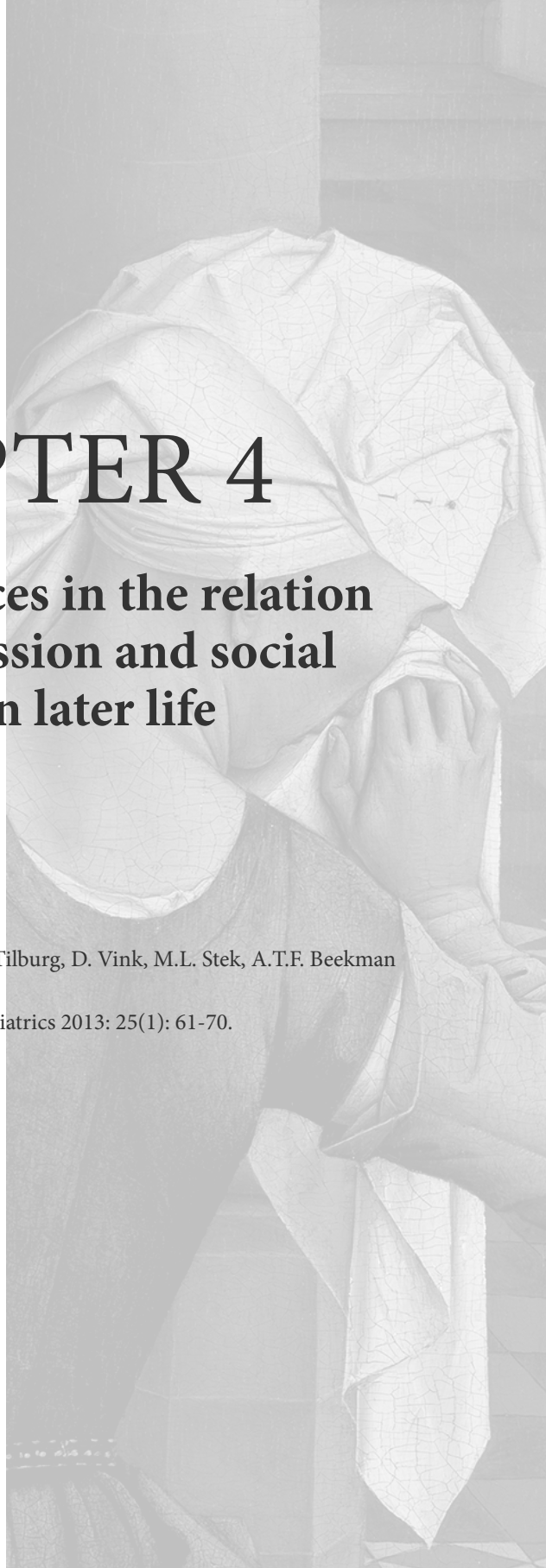

CHAPTER 4

Gender differences in the relation between depression and social support in later life

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International Psychogeriatrics 2013: 25(1): 61-70.

ABSTRACT

Background

Prevalence of depression is twice as high in women as in men, also in older adults. Lack of social support is a risk factor for late life depression. The relation between depression and social support may be different for men and women.

Methods

Data from the Longitudinal Aging Study Amsterdam were used to investigate gender differences in the relation between social support and depression in a population-based sample aged 55-85 years, with n = 2823 at baseline and using 13-year follow-up data on onset of depression.

Results

Respondents without a partner in the household, with a small network and with low emotional support were more often depressed, with men showing higher rates of depression than women. High need for affiliation was associated with depression in women but not in men. Lack of a partner in the household and having a small network predicted onset of depression in men but not in women. In respondents with high affiliation need and low social support depression rates were higher, with men being more often depressed than women.

Conclusions

Low social support and a high need for affiliation were related to depression in later life, with men being more vulnerable for depression than women. Considering the serious consequences of depression, especially in older people, it is important to identify the persons with low social support and a high need for affiliation, and to help them to increase their social support, or to adjust their needs.

INTRODUCTION

Life-time prevalence of depression in adult women is almost of twice that in men (21% and 13%, respectively) (Weissman and Klerman 1977; Jorm 1987; Kessler, McGonagle et al. 1993; Wolk and Weismann 1995; Bebbington, Dunn et al. 1998; Kessler 2006). Furthermore, women have higher relapse or non-remission rates (Kuehner 2003). Possible explanations of this gender disparity (the so-called 'gender gap') in depression are sex differences in social factors, such as social role and status, life-events and social support, in addition to sex differences in biological factors (genetic vulnerability, hormonal influences) and psychological factors (coping style, neuroticism, mastery) (Kessler and McLeod 1984; Wolk and Weismann 1995; Dorn and Chrousos 1997; Nolen-Hoeksema 2000; Kendler, Thornton et al. 2001; Kuehner 2003; Kooiman, Jansen et al. 2007; Leach, Christensen et al. 2008).

Some authors have concluded that the gender gap is associated with the reproductive period of life, and that in older age the gender-gap diminishes or disappears (Krause 1986; Jorm 1987; Bebbington, Dunn et al. 1998; Noble 2005), but other studies failed to confirm this hypothesis (Beekman, Copeland et al. 1999; Prince, Beekman et al. 1999; Sonnenberg, Beekman et al. 2000; Cairney and Wade 2002). Among the explanations for the persisting gender gap in older age is the differential exposure of older men and women to social risk factors for late life depression (Sonnenberg, Beekman et al. 2000). Older women have lower education and income than older men, and they are more likely than men to lose their partner, which is an important risk factor for depression (Harlow, Goldberg et al. 1991; Mendes de Leon, Kasl et al. 1994). However, not only a differential exposure to risk factors is likely to play a role, but the impact of risk factors also shows gender differences. Older women appear to be less vulnerable for depression than older men when they lose their partner, and when they receive little emotional support (Umberson, Wortman et al. 1992; van Grootheest, Beekman et al. 1999; Sonnenberg, Beekman et al. 2000). Therefore, not only the amount, but also the significance of interpersonal relationships and social support may influence gender differences in depression, their effects being in different directions.

In studies on social ties among adults of all ages, women and men were found to have a different need for social affiliation, and different expectations of social relationships. Women of all ages have a larger personal network and receive more social support, which is a protective factor against depression, but which also provides a greater opportunity for negative interpersonal experiences (e.g. death of someone close), which in turn may lead to

depression (Kessler and McLeod 1984; Kendler, Thornton et al. 2001; Leach, Christensen et al. 2008). In a study by Dalgard and coworkers women experienced more negative life events, particularly related to their personal network, but also had more support, both in general and in the context of the event. Also, women with little support were more vulnerable to depression than men in case of a life event (Dalgard, Dowrick et al. 2006). Husbands and wives were found to provide equal support to each other, but women felt more responsible than men towards their spouse as well as towards other persons, which may lead to feelings of being burdened and overloaded (Neff and Karney 2005). Interpersonal problems with one's family are associated with a higher prevalence of depression in women than in men, probably due to a greater involvement and feelings of responsibility in family matters in women (Leach, Christensen et al. 2008).

Similar evidence has been reported on older persons. Older women were found to be more sensitive to life events occurring to other persons than older men (Kessler and McLeod, 1984; Maciejewski, Prigerson et al. 2001). In older people, social support protected against psychological distress, but in older women with low resources, social connections increased levels of distress, particularly if there was role strain due to obligations to provide support to others (Kawachi and Berkman 2001). In another study on coping with functional diseases in older married couples aged 60-84, social support led to improved well-being in men but not in women (Robb, Small et al. 2008). In a study of people aged 40–70 years old, Takizawa found that men benefited from social support as buffer against depression, but women did not (Takizawa, Kondo et al. 2006). In a study of 600 African-American older community residents (aged 55-85 years) women tended to become more depressed with increasing number of events combined with low levels of social attachment, guidance and reliability, particularly when they were living alone (Husaini, Moore et al. 1991).

In summary, women have generally been found to have a larger network, which is associated with more social support, but they also experience more negative impact of their social relationships than men. The gender differences in need for social affiliation may be a reflection of differences in the need for sharing feelings, problems and life-events, and in the appreciation and the expectations of the existing relationships and support. It is important to note that depression may also enhance the felt need for affiliation through specific symptoms such as feeling lonely or feeling helpless. Because depression, gender, need for social affiliation and actual social support are intertwined, prospective designs are needed to study the influence of the presence or absence of social support and need for affiliation on the onset of depression in men and women.

In older people many changes in social support take place, due to changes in health, functional capacity and living arrangements, and to illness or death of important others. Therefore, studies focusing on older age are useful to obtain a better understanding of the protective and disruptive effects of social relationships on distress and depression in later life, and lead to a more individually tailored approach in the management of these mental health problems in older men and women.

In the present study, we aimed to investigate the relation between social support (amount of social support and need for social affiliation) and late-life depression in men and women, both in a cross-sectional and prospective design, in a community-based sample of older Dutch citizens.

MATERIALS AND METHODS

Sampling and procedures

Data were derived from the Longitudinal Aging Study Amsterdam (LASA), an ongoing interdisciplinary study on predictors and consequences of changes in autonomy and well-being in the aging population (Deeg and Westendorp-de Serière 1994) (Deeg, van Tilburg et al. 2002). Details on sampling procedures and response have been described in previous publications (Beekman, Deeg et al. 1995; Beekman, Geerlings et al. 2002; Deeg, van Tilburg et al. 2002; Vink, Aartsen et al. 2009). Briefly, the LASA-cohort is based on a representative sample of 3107 older adults between the ages of 55 and 85 at baseline, stratified for age and sex. It was drawn from the population registers of 11 municipalities in three regions of the Netherlands.

Data collection started in 1992-1993 (T1), followed by data collection cycles every three years: in 1995-1996 (T2), 1998-1999 (T3), 2001-2002 (T4) and 2005-2006 (T5). Trained and supervised interviewers using the same procedures and instruments interviewed respondents at home. All interviews were tape-recorded. The numbers of participants in the five cycles were 3107, 2545, 2076, 1691 and 1257, respectively. Non-response in the first LASA-cycle was associated with age, but not with sex. Attrition between T1 and T5 was mainly due to mortality: percentages of people who died before approach were 13% between T1 and T2, 14% between T2 and T3, 14% between T3 and T4 and 14% between T4 and T5. Other reasons for attrition were refusal, frailty and failure to contact (about 5% per cycle). At all four follow-up cycles, attrition was associated with older age and male sex, and with physical disease and cognitive impairment at the preceding cycle. Attrition at T2

was associated with a low level of education and to the presence of depression at T1 but this pattern was not observed at later cycles.

For the present cross-sectional investigation of the association between social support and depression, and gender differences in these associations, the data of the first LASA-cycle were used. Due to incomplete data on social support or on the need for social attachment, 2823 out of the 3107 respondents were available for the analyses. Furthermore, we conducted a longitudinal investigation of the association of social support with onset of depression in the follow-up period, for which follow-up data were used of respondents who were not depressed at T1 according to the Centre for Epidemiologic Studies Depression scale (CES-D≤12), and had at least one follow-up measurement. 1928 respondents fulfilled these criteria. At the four follow-up measurements the numbers of available respondents were 1858, 1580, 1253 and 910, respectively.

Measures

Depression

Depressive symptoms were measured with the Centre for Epidemiologic Studies Depression scale (CES-D), a 20-item self-report scale developed for use in the community (Radloff 1977; Radloff and Teri 1986). The CES-D has good psychometric properties in older community samples (Beekman, Deeg et al. 1997) with minimal overlap with physical illness (Berkman, Berkman et al. 1986). Scores range from 0 to 60 and respondents scoring 16 or higher were considered to have a clinically relevant level of depressive symptoms. At baseline, prevalence of depression was established based on the CES-D. In the prospective study, onset of depression was defined as the development of depression, defined as crossing the cut-off score of the CES-D with an increase of at least 4 points at one or more measurements within the thirteen years of follow-up.

Social and personal support

Three aspects of social and personal support were measured.

First, the *presence of a partner in the household* was assessed. A partner is generally considered the most important relationship in the social network. When the partner is available, he or she is generally an important resource of support (Ross, Mirowsky et al. 1983; Turner and Marino 1994). Respondents received a score of 1 if a spouse or someone they considered their partner was available in the household, otherwise 0.

Next, *personal network size* was measured, defined as the total number of network members with whom the respondent had important and regular contact (van Tilburg 1998). Network size ranged from 0 to 75 network members, with a mean of 14 and a median of 12 network members. A network with less than 11 network members was considered to be small.

In addition to these structural aspects of social support, functional support exchanges within social relationships were also measured. For this study, we used the mean amount of *emotional support* received from the maximally nine network members (excluding the partner) with whom contact was most frequent. Respondents were asked how often in the previous year they had talked to these nine network members about personal experiences and feelings. Response categories were never (0), seldom (1), sometimes (2) and often (3). Mean scores of the emotional support received from the nine network members were computed and divided in three groups ranging from 0 (relationships are seldom or never supportive) to 2 (relationships are often supportive) (Penninx, van Tilburg et al. 1999). For this study, respondents in the groups with scores of 0 or 1 were considered to have low received emotional support.

Need for social affiliation

The need for social affiliation was measured with a 4-item self-report scale, the need for affiliation scale. This scale was developed and tested in an adult Dutch community sample (Van Tilburg 1988), and contains questions about the need to talk to others about one's feelings, the need for help and support in case of trouble, the need to go to others when something bothers the respondent, and the need to lean on someone when experiencing difficulties. Scores range from 4 (low need for affiliation) to 12 (strong need for affiliation), and respondents scoring 9 or higher were considered to have a high need for affiliation. Reliability of this scale was sufficient, with a Cronbach's Alpha of 0.73.

Age, gender, level of education, cognitive impairment and physical limitations were considered to be potential confounders because of their relation to depression, gender and social support, and were therefore included in the study. Respondents were divided into three age groups: 55-64, 65-74 and 75-85 years old. Education was ranked according to three levels: elementary education, intermediate or secondary (vocational) education, and high (vocational) education including university and college education. Cognitive impairment was measured with the Mini-Mental State Examination (MMSE) using a cut-off score of 23 (Folstein, Folstein et al. 1975). Physical limitations were measured with a self-report

scale on difficulty with several activities of daily functioning, previously validated in the Netherlands and summarised in two categories: no difficulty and difficulty with one or more activities (Van Sonsbeek 1988); (Kriegsman, Deeg et al. 1997).

Statistical analyses

Baseline sample characteristics were assessed, including prevalence of depression, in the full sample, and in men and women separately, using chi square statistics and logistic regression analyses to indicate the magnitude of the gender differences.

Bivariate associations of depression with each of the three social support measures and affiliation need were investigated, adjusted for age and gender, and calculating odds ratios in the full sample and in both genders. In order to control for possible confounding, multivariate analyses were performed for each of the support measures and affiliation need, including age, gender, level of education, cognitive impairment and functional limitations as independent variables. Testing for interaction effects of gender on these associations was performed, using logistic regression analyses.

To investigate the prospective associations of each of the social support measures and need for affiliation with onset of depression, Cox regression analyses were performed in the sample of respondents who were not depressed at the first LASA-cycle, with time to onset of depression during follow-up as the dependent variable, and adjusted for age and gender. In order to control for the confounding variables as mentioned above, multivariate analyses were performed.. Testing for interaction effects of gender on these associations was performed, using logistic regression analyses.

In all analyses, the criterion for statistical significance was $p < 0.05$.

RESULTS

An overview of baseline sample characteristics with gender differences is shown in Table 1. Due to the stratified sampling, age and gender were equally distributed in the sample. Most respondents had low or intermediate levels of education, with significantly more women in the low-level group. Cognitive impairment was equally divided between men and women. 40% had one or more physical limitations, with preponderance in women. Half of the respondents had a partner in the household. Network size ranged from 0 to 75, with a mean of 14 network members. The majority received emotional support on a regular basis,

Table 1. Characteristics of LASA baseline sample (N=2823) with gender differences

	Full sample (n = 2823)		Men (n = 1369)		Women (n = 1454)		p-value of gender difference
	N	%	N	%	N	%	
Sex:							
Male	1369	48.5					
Female	1454	51.5					
Age:							
55-64	932	33.0	449	32.8	483	33.2	p = 0.40
65-74	899	31.8	423	30.9	476	32.7	
75-85	992	35.2	497	36.3	495	34.1	
Level of education:							
Low (elementary)	1195	42.3	425	31.0	770	53.0	**p < 0.001**
Intermediate	1300	46.1	726	53.0	574	39.5	
High	328	11.3	218	16.0	110	7.5	
Cognitive functioning:							
Not impaired (MMSE ≥ 24	2438	86.4	1184	86.5	1254	86.2	p = 0.97
Impaired (MMSE < 24)	385	13.6	185	13.5	200	13.8	
Physical limitations:							
No	1706	60.4	918	67.1	788	54.2	**p < 0.001**
One or more	1117	39.6	451	32.9	666	45.8	
Partner available in household:							
No partner	897	31.8	234	17.1	663	45.6	**p < 0.001**
Partner in household	1844	65.3	1086	79.3	758	52.1	
Partner out household	82	2.9	49	3.6	33	2.3	
Network size (range 0-75):							
Mean (SD)	13.9(8.3)		13.8		14.0		p = 0.49
Small (< 11)	1156	40.9	580	42.4	576	39.6	p = 0.14
Emotional support received							
Seldom	584	20.7	356	26.0	228	15.7	
Sometimes	1254	44.4	614	44.9	640	44.0	**p < 0.001**
Often	985	34.9	399	29.1	586	40.3	
Need for affiliation:							
Low (score 4-8)	1464	51.9	774	56.5	690	47.5	**p < 0.001**
High (score 9-12)	1359	48.1	595	43.5	764	52.5	
Depressive syndrome:							
No (CESD <16)	2449	86.8	1236	90.3	1213	83.4	**p < 0.001**
Yes (CESD ≥ 16)	374	13.2	133	9.7	241	16.6	

half of which often. As expected, statistically significant gender differences were found for two social support variables, with men having more often a partner in the household and women receiving more emotional support. Need for affiliation was significantly higher in women than in men. 13% of the respondents had depressive symptoms according to the CES-D, with a statistically significant gender difference of 16.6% in women and 9.7% in men (OR=1.87, CI = 1.49-2.34, p<0.001, adjusted for age).

Table 2 shows the results of bivariate analyses of depression with the three social support measures and affiliation need, adjusted for age and gender. Not having a partner in the household and having a small network size were both associated with depression in the full sample, and in men and in women separately. Low emotional support received was associated with depression in men, but not in women or in the full sample. A high need for social affiliation was associated with depression in the full sample and in women, but not in men. Gender differences in these associations were statistically significant (OR laying outside the CI of the other gender) for having no partner in the household and low emotional support, with men in these conditions being more vulnerable for depression than women.

Table 2. Bivariate associations of depression with social support and need for affiliation, adjusted for age and gender, in the full sample and in men and women (OR with 95% CI)

	Full sample (n = 2823)			**Men (n = 1369)**			**Women (n = 1454)**		
	OR	**CI**	***p***	**OR**	**CI**	***p***	**OR**	**CI**	***p***
No partner in household	**2.72**	**2.13-3.47**	**p<0.001**	**4.01**	**2.76-5.88**	**p<0.001**	**2.06**	**1.52-2.81**	**p<0.001**
Small network (< 11)	**1.68**	**1.34-2.10**	**p<0.001**	**1.97**	**1.37-2.84**	**p<0.001**	**1.51**	**1.14-2.00**	**p<0.01**
Low emotional support received	1.06	0.84-1.33	p=0.65	**1.62**	**1.05-2.50**	**p=0.03**	0.85	0.64-1.12	p=0.24
High affiliation need (>8)	**1.32**	**1.06-1.64**	**p=0.02**	1.27	0.89-1.82	p=0.19	**1.37**	**1.03-1.82**	**p=0.03**

In table 3, results are shown of the multivariate analyses of depression with the three social support measures and affiliation need, controlling for the confounding variables age, gender, level of education, cognitive impairment and functional limitations. Not having

partner in the household and having a small network size remained statistically significant in the association with depression in the full sample and in men and women separately. Low emotional support received was associated with depression in men but not in the full sample or in women. High need for affiliation was associated with depression in the full sample and in women, but not in men. Statistically significant gender differences in these associations were found for having no partner in the household and low received emotional support. Test statistics of the interactions for gender are shown in the footnotes of table 3.

Table 3. Multivariate associations of depression with social support and need for affiliation, adjusted for age, gender, level of education, cognitive impairment and functional limitations, in the full sample and in men and women (OR with 95% CI)

	Full sample (n = 2823)			**Men (n = 1369)**			**Women (n = 1454)**		
	OR	**CI**	***p***	**OR**	**CI**	***p***	**OR**	**CI**	***p***
No partner in household (*1)	**2.43**	**1.89-3.13**	**p<0.001**	**3.34**	**2.25-4.96**	**p<0.001**	**1.97**	**1.43-2.72**	**p<0.001**
Small network (< 11) (*2)	**1.51**	**1.20-1.90**	**p<0.01**	**1.73**	**1.19-2.52**	**p<0.01**	**1.38**	**1.03-1.86**	**p<0.03**
Low emotional support received (*3)	1.01	0.80-1.29	p=0.92	**1.58**	**1.01-2.47**	**p<0.05**	0.82	0.61-1.10	p=0.18
High affiliation need (>8) (*4)	**1.37**	**1.09-1.72**	**p<0.01**	1.17	0.81-1.70	p=0.40	**1.50**	**1.12-2.02**	**p<0.01**

Interactions of gender with:

*1. no partner in the household: **OR=1.72, CI=1.06-2.80, *p*=0.03**

*2. small network size: OR=1.28, CI=0.80-2.04, *p*=0.31

*3. low emotional support received: **OR=1.93, CI=1.13-3.29, *p*=0.02**

*4. high affiliation need: OR=1.01, CI=0.92-1.11, *p*=0.85

In Table 4 the results for onset of depression in the follow-up sample are shown, adjusted for age and gender. In the Cox regression analyses in the sample without depression at baseline (CESD ≤ 12) a higher onset of depression in the follow-up period of 13 years was found in respondents without a partner in the household and in those with a small network

at baseline, , but not in respondents with low emotional support, or with a high affiliation need. Separate analyses for men and women showed a statistically significant association with onset of depression for living without a partner in the household and for having a small network in men, but not in women.

Table 4. Cox regression analyses with hazard ratios with 95% confidence intervals of onset of depression with social support and need for affiliation, adjusted for age and gender, in the full sample and in men and women

	Full sample (n = 1928)			**Men (n = 945)**			**Women (n =983)**		
	HR	**CI**	***p***	**HR**	**CI**	***p***	**HR**	**CI**	***p***
No partner in household	**1.23**	**1.00-1.51-1.44**	**p<0.05**	**1.87**	**1.31-2.66**	**P<0.01**	1.08	0.84-1.37	p=0.56
Small network (< 11)	**1.33**	**1.10-1.60**	**p<0.01**	**1.82**	**1.33-2.48**	**p<0.01**	1.13	0.89-1.43	p=0.33
Low emotional support received	0.89	0.73-1.07	p=0.21	0.89	0.64-1.25	p=0.51	0.90	0.72-1.13	p=0.38
High affiliation need (>8)	1.15	0.96 -1.39	p=0.13	0.98	0.72-1.34	p=0.91	1.23	0.98-1.55	p=0.08

In Table 5 the results the multivariate analyses for onset of depression in the follow-up sample are shown, with controlling for the confounding variables. In the Cox regression analyses in the sample without depression at baseline (CESD ≤ 12) a higher onset of depression in the follow-up period of 13 years was found in respondents with a small network at baseline, but not in respondents without a partner in the household, with low emotional support, or with a high affiliation need. Separate analyses for men and women showed an association with onset of depression for living without a partner in the household and for having a small network in men, but not in women.

A statistically significant interaction effect of gender on onset of depression was found for not having a partner in the household and for small network size, with men being more likely to become depressed than women with these characteristics. Test statistics of the interactions for gender are shown in the footnotes of table 5.

Table 5. Cox regression analyses with hazard ratios with 95% confidence intervals of onset of depression with social support and need for affiliation, adjusted for age, gender, level of education, cognitive impairment and functional limitations, in the full sample and in men and women

	Full sample (n = 1928)			**Men (n = 945)**			**Women (n =983)**		
	HR	**CI**	***p***	**HR**	**CI**	***p***	**HR**	**CI**	***p***
No partner in household (*1)	1.17	0.95-1.45	p=0.14	**1.70**	**1.19-2.43**	**P<0.01**	1.06	0.82-1.35	p=0.67
Small network (< 11) (*2)	**1.29**	**1.07-1.55**	**p<0.01**	**1.71**	**1.25-2.34**	**p<0.01**	1.10	0.87-1.40	p=0.44
Low emotional support received (*3)	0.85	0.70-1.03	p=0.10	0.87	0.62-1.21	p=0.40	0.86	0.68-1.09	p=0.21
High affiliation need (>8) (*4)	1.13	0.94 -1.36	p=0.19	0.97	0.71-1.32	p=0.83	1.20	0.95-1.52	p=0.13

Interactions of gender with:

*1. no partner in the household: **HR=1.99, CI=1.32-3.00, *p*<0.01**

*2. small network size: **HR=1.69, CI=1.15-2.50, *p*<0.01**

*3. low emotional support received: HR=0.89, CI=0.44-1.81, *p*=0.74

*4. high affiliation need: HR=1.27, CI=0.87-1.88, *p*=0.22

DISCUSSION

In the present study on gender differences in the relation between social support and depression in a population sample of 2823 Dutch citizens aged 55-85 years, we observed associations of depression in later life with several social support measures and need for social affiliation, and gender differences in these associations.

Women were found to be more often depressed than men. Respondents without a partner in the household and with a small network showed higher depression rates than those living with a partner and with a large network. These findings correspond with the literature on depression in the elderly (Blazer 1989; Harlow, Goldberg et al. 1991; 1992; Copeland, Davidson et al. 1992; Blazer, Kessler et al. 1994; Mendes de Leon, Kasl et al. 1994; Beekman, Deeg et al. 1995; Cole, Bellavance et al. 1999; Cole and Dendukuri 2003). Depression was

also associated with having a high need for social affiliation. These associations persisted after adjustment for age, gender, education, cognitive impairment and functional limitations.

Although women were found to be more often depressed than men, the associations between depression and some of the social support measures were stronger for men than for women. Men without a partner in the household or with low emotional support received were more vulnerable for depression than women. Vulnerability for depression associated with a small network size was equal for men and women. On the other hand, a high need for affiliation was associated with depression only in women and not in men.

In the prospective analyses, male respondents living without a partner in the household and having a small network were more likely to experience onset of depression than women.

So, men without a partner in the household appeared to be more vulnerable for prevalence and onset of depression than women. However, due to more frequent partner loss, women experience the lack of a partner in the household more often than men, which explains the female preponderance in depression in this respect.

Considering the role of need for affiliation, older persons with a high need for affiliation were found to be more likely to have depression than those with a low affiliation need. As noted earlier, an explanation of this finding may be, that people who are depressed have higher scores on affiliation need, because they feel more in need for support due to their low mood. Thus, a high affiliation need may be part of the depressive syndrome. Our finding that having a higher need for affiliation did not predict the onset of depression provides some support for this explanation. In the literature, need for affiliation is not considered to be a fixed personality trait, but a lasting pattern of conceptions about what is needed and desirable for a person. When one's personal circumstances are not in accordance with these needs and wishes, people may attempt to adjust their situation (e.g. by searching for new friends or a new partner), or they may lower their expectations about what they need (e.g. accepting that one has no partner anymore, and that this resource of support is no longer available). Changes in the need for affiliation are supposed to take time, and the capacity to change is likely to show considerable interpersonal variation. It is conceivable that particularly those persons who have a high affiliation need and are incapable to adjust this need to a lower level when social support has declined, are at risk for depression. Our results showed that low support - a well-known risk factor for depression - and high need for social affiliation both increased the risk for depression, and they may enhance each other.

In our study sample, 351 respondents had low social support, and 79 of these respondents had a high need for affiliation. One third of these were men. In this group with low support combined with a high affiliation need, 29.1% was depressed, with a preponderance in men (34.6%) compared to women (26.4%). These gender differences were not statistically significant, due to the small numbers, but these percentages are much higher than in the full sample, particularly in men, and they may be of clinical importance. So when aiming to identify older persons at risk for depression for preventive strategies, we should target the subgroup with low support and with a high affiliation need.

Strengths and limitations

Strengths of the present study include its large sample size, with comparatively low attrition at follow-up, and its balanced gender ratio, especially in older age groups.

In addition, several potential limitations need also be addressed. We investigated the quality of the social network mostly by applying quantitative measures: the availability of a partner and the network size. Although we asked the respondents to identify important network members only, it is possible that the respondent was not satisfied about the content and the quality of these factors. A person may have a small but very supportive network, or alternatively a large but superficial network and/or a not very supportive spouse. To minimise these problems we included a third measure, received emotional support, which reflected the quality of the relationship. Another problem may be that we underestimated the true prevalence of depression in the follow-up sample due to the fluctuating course of depression relative to the three-year interval between every follow-up cycle.

Conclusion

Older women had a higher prevalence of depression than older men. Older people without a partner in the household, with a small network and with low emotional support were more likely to experience depression, with men having higher rates of depression than women in these conditions. A high need for social affiliation was associated with depression, but only in women. Lack of a partner in the household and having a small network predicted onset of depression in men but not in women. In a subgroup with low social support and high affiliation need, high rates of depression were found, particularly in men. Considering the serious consequences of depression, it is important to focus on older people with these characteristics, with the aim of helping them to increase their social support, or to accept the deficiency in support and adjust their needs.

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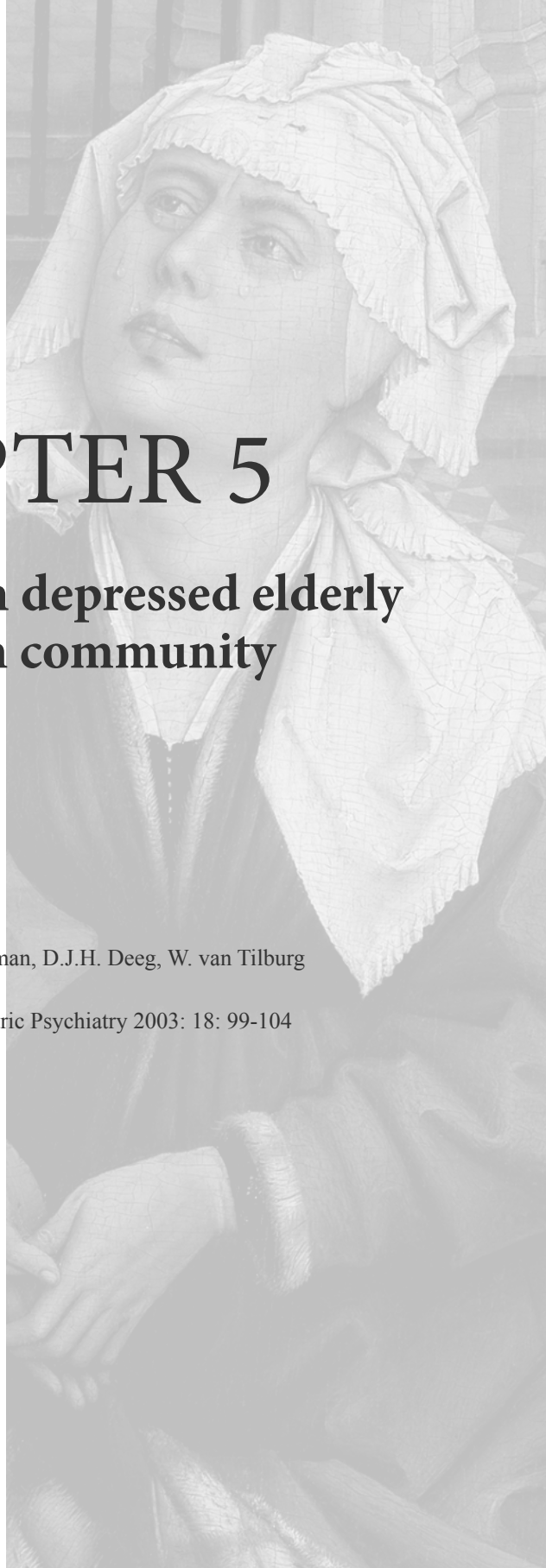

CHAPTER 5

Drug treatment in depressed elderly in the Dutch community

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International Journal of Geriatric Psychiatry 2003: 18: 99-104

ABSTRACT

Objectives

In older people, a diagnosis of depression is frequently missed, and proper treatment is subsequently hampered. We investigated antidepressant and benzodiazepine use in an older community sample, and assessed possible risk factors associated with non-treatment in depressed elderly.

Methods

Data were used from the baseline measurements of the Longitudinal Aging Study Amsterdam (LASA). In a random, age and sex stratified community sample of 3107 older Dutch people (55 to 85 years), respondents were screened on depression with the Center for Epidemiologic Studies Depression Scale (CES-D). In the depressed subsample depressive disorder according to DSM-III was assessed using the Diagnostic Interview Schedule (DIS). The use of antidepressants and anxiolytics (benzodiazepines) in the depressed subsample was measured, and associations with age, sex, cognitive impairment, physical health and anxiety symptoms were investigated.

Results

Only 16% of the respondents with a major depressive disorder used antidepressants. More than half of them used non-therapeutic dosages. Lower antidepressant use was associated with cognitive impairment. Benzodiazepine use was more likely than antidepressant use, which was especially evident in females in the major depressive disorder group.

Conclusions

Depressed older people were undertreated, particularly when they were cognitively impaired. A high rate of benzodiazepine use was found, particularly in females.

INTRODUCTION

Depression is an important disorder in later life: the prevalence of clinically relevant depression in older persons is about 14 % (Copeland, Dewey et al. 1987; Livingston, Hawkins et al. 1990; Blazer 1994; Beekman, Copeland et al. 1999). There is a good response to treatment, also in the elderly (Hinrichsen 1992; Reynolds, Frank et al. 1994; Schneider, Reynolds et al. 1994; Reynolds, Frank et al. 1996; Little, Reynolds et al. 1998; Miller, Cornes et al. 2001). However, several studies show undertreatment in older people with depression (Copeland, Davidson et al. 1992; Katon, von Korff et al. 1992; Blanchard, Waterreus et al. 1994; Koenig, George et al. 1997; Cole, Bellavance et al. 1999; Wilson, Copeland et al. 1999). Difficulties in diagnosing depression in the elderly probably play a role in this undertreatment. In later life, the majority of depressive episodes do not fulfill DSM criteria for major depression (Blazer, Kessler et al. 1994; Tannock and Katona 1995). Other diagnostic problems are a high co-incidence of anxiety symptoms, somatic comorbidity and cognitive impairment (Sunderland, Alterman et al. 1988; Blazer, Kessler et al. 1994; Streim, Oslin et al. 2000). Particularly the presence of sleep disturbances and anxiety symptoms can lead to the prescription of hypnotics and anxiolytics (mostly benzodiazepines) instead of antidepressants (Brown, Sweeney et al. 1984; Copeland, Davidson et al. 1992).

Furthermore, depression is sometimes looked upon as a normal reaction to stress (losses, physical decline) or to getting older, and thus not in need of specific treatment (Lindesay, Briggs et al. 1989). In the presence of cognitive impairment or physical illness, specific antidepressant treatment may be considered less appropriate or even harmful.

There are several studies of pharmacological treatment of depression in the elderly, but community-based studies of predictors of (non)treatment are rare (Brown, Salive et al. 1995; Newman and Hassan 1999; Wilson, Copeland et al. 1999).

The aim of the present study was to investigate pharmacological treatment (antidepressants and benzodiazepines) in depressed older persons in the Dutch community. It was hypothesized that antidepressant use would be low, particularly in the very old and in the group with physical problems or cognitive impairment, but would rise with increasing severity of the depression. Antidepressant use was expected to be higher than in Anglo-Saxon countries, because in the Netherlands GP-coverage of the older population is virtually 100% and Dutch people are highly likely to visit their GP when they are depressed. Benzodiazepines

were expected to be commonly prescribed, and more often to women than to men, as has been found in studies of younger adults (van der Waals, Mohrs et al. 1993).

MATERIALS AND METHODS

Sample and procedures

Data were derived from the baseline cycle of the Longitudinal Aging Study Amsterdam (LASA), an interdisciplinary study on the predictors and consequences of changes in autonomy and well-being in the aging population (Deeg and Westendorp-de Seriere 1994). Sampling procedures and characteristics of the sample have been described in detail in previous publications (Beekman, Deeg et al. 1995). In short, the LASA cohort is based on a representative random sample of older adults between the ages of 55 and 85, stratified for age, sex and expected mortality five years into the study. It was drawn from the population registers of 11 municipalities in three regions of the Netherlands, and was also used in another study 10 months prior to LASA (NESTOR-LSN, n = 3805, response-rate 62.3%). Of the 3805 LSN-participants, 3107 participated in LASA (response rate 81.7%). Non-response was related to age (partly due to illness or cognitive impairment), but not to sex. Due to item-nonresponse (more than 2 missing items on the depression-scale) 51 participants were lost, leaving a baseline sample of 3056.

In this baseline sample depression was measured in a two-stage design. All subjects scoring $^{3}16$ on the Center for Epidemiologic Studies Depression scale (CES-D, Radloff 1977), and a similarly sized random sample of those scoring < 16 were approached for an additional, diagnostic interview, scheduled 2 to 8 weeks after the LASA-baseline interview. Response was 86%; resulting in 660 complete diagnostic interviews. Response was related to age but not to sex. In this diagnostic subsample depressive disorders were measured using the Diagnostic Interview Schedule (DIS) (Robins, Helzer et al. 1981). This two-stage design has been described in detail elsewhere (Beekman, Deeg et al. 1997). In the diagnostic sample 330 respondents met criteria for a depressive syndrome according to CES-D or DIS. In 3 respondents, data about medication use were not available, thus resulting in a study sample of 327.

Measures

(1) Definition and measurement of depression

Depressive symptoms were measured with the Center for Epidemiologic Studies Depression scale (CES-D), a 20 item self-report scale developed for use in the community (Radloff 1977; Radloff and Teri 1986). The CES-D had good psychometric properties in elderly community samples, also in the Dutch translation (Beekman, Deeg et al. 1997). There is a minimal overlap with physical illness (Berkman, Berkman et al. 1986). Scores range from 0-60. Respondents scoring 16 or higher on this scale are considered to have a clinically relevant level of symptoms. Using this cut-off point the CES-D had a very good criterion validity for major depressive disorder (Beekman, Deeg et al. 1997).

In the diagnostic subsample DSM-III diagnoses of dysthymia and major depressive disorder (6-month prevalence) were reached using the Diagnostic Interview Schedule (DIS) (Robins, Helzer et al. 1981). This is a widely used diagnostic instrument, designed for use in epidemiological studies.

Based on the CES-D and the DIS three subgroups were distinguished: major depressive disorder (MDD), dysthymia (DYSTH) and a subthreshold depression group with depression according to the CES-D but not fulfilling diagnostic criteria (SUBTHR).

(2) Pharmacological treatment

Pharmacological treatment was assessed by recording the medication of the participants directly from the containers in the home of the respondents. The anatomical-therapeutical-chemical coding and categorization system for medication (Pahor, Chrischilles et al. 1994) was used to classify antidepressants and benzodiazepines; within the latter group only anxiolytics were used. Daily dosage of the antidepressant was investigated and scored in four categories: not known, not therapeutic, maybe therapeutic, and therapeutic.

(3) Co-variates

Age was used in three age groups: 55-64, 65-74 and 75-85 years old.

Cognitive impairment was measured with the Mini Mental Status Examination (Folstein, Folstein et al 1975), using a cut-off of 23.

Physical health was assessed using a detailed questionnaire on chronic physical diseases (CBS 1989). In order to investigate the possible misclassification due to self-report, data

were cross-checked with general practitioners. There was no influence of depressive symptomatology on the agreement between patients and GPs (Kriegsman, Penninx et al. 1996). Functional limitations were measured using an ADL-scale previously validated in the Netherlands (van Sonsbeek 1988).

To investigate anxiety symptoms the anxiety section of the Hospital Anxiety and Depression Scale (HADS-A) (Zigmond and Snaith 1983) was used. This is a 7-item self-rating scale, designed for measuring anxiety symptoms in samples with somatic comorbidity.

Data-analysis.

Treatment with antidepressant medication was investigated in the full sample and in the three depressed groups, using chi-square statistics. To investigate the influence of the severity of the depression, the association between CES-D-score and antidepressant use was calculated in bivariate analyses in the full sample, using logistic regression.

The association of antidepressant use and age was investigated in bivariate analyses, using logistic regression.

Sex differences in antidepressant use and associations of antidepressant use with physical health problems and cognitive impairment in the full sample and in the three groups were assessed in bivariate analyses, using odds ratios with 95% confidence intervals.

Benzodiazepine use was investigated in the three groups with chi-square statistics. The association of benzodiazepine use with sex, antidepressant use and anxiety symptoms were examined in bivariate analyses, using odds ratios with 95% confidence intervals.

RESULTS

Description of the sample.

In Table 1, demographic and health-related characteristics of the study sample are shown. The female preponderance in the study sample is in accordance with the sex differences that are found in the prevalence of depression (Sonnenberg, Beekman et al. 2000).

Table 1. Characteristics of the depressed sample (n=327)

Variables	n	%
Age (years)		
55-64	85	26.0
65-74	94	28.7
75-85	148	45.3
Sex		
Male	118	36.1
Female	209	63.9
Marital status		
Married	137	41.9
Not married	190	58.1
Cognitive functioning		
MMSE<24	49	15.0
MMSE 24-30	276	84.4
Depressive symptoms /disorder		
Major depression	55	16.9
Dysthymia	25	7.6
Subthreshold depression	247	75.5
Chronic physical illness		
None	69	21.1
One or more	256	78.3
Physical limitations		
None	111	33.9
One or more	211	64.5
Anxiety complaints		
No (HADS-A 0-7)	165	50.5
Yes (HADS-A 8-21)	137	41.9

Antidepressant use; sex differences.

Table 2 shows antidepressant use in the full sample and in the three depressed groups, in both sexes. Generally, antidepressant use was low: 4.9%. In the major depressive disorder group the highest rates were found: 16.4%. In this group there was a suggestion of sex difference in favor of men: antidepressant use in men in this group was almost twice as high as in women: 25% versus 14 %, but the odds ratio was not statistically significant (OR = 2.1; C.I. = 0.4 - 9.8).

In the subthreshold depression group antidepressant use was very low (2.4%), both in males and in females. In the dysthymia group antidepressant use was almost nonexistent and too small for further statistical analyses.

Table 2. antidepressant use (AD) in the depressed groups

	All			males			females		
	n	**AD**	**%AD**	**n**	**AD**	**%AD**	**n**	**AD**	**%AD**
SUBTHR	247	6	2.4%	99	2	2.0%	148	4	2.7%
DYSTH	25	1	4.0%	7	0	0%	18	1	5.6%
MDD	55	9	16.4%	12	3	25%	43	6	14%
TOTAL	327	16	4.9%	118	5	4.2 %	209	11	5.3%

Considering the daily doses of the antidepressant, only 4 out of the 16 antidepressant users (25%) had a daily dose that was considered to be therapeutic; another 3 (20%) had a daily dose that may be therapeutic.

In the full sample a statistically significant association between antidepressant use and increasing CES-D-scores was found: B=0.08; SE=0.03; p=0.007.

Association of antidepressant use with age, physical health problems and cognitive impairment.

In the full sample an inverse trend between antidepressant use and age was found: B= -0.58, SE=0.31, p=0.06.

In the full sample no association of antidepressant use with cognitive impairment was found. However, within the major depression group 18% of those with MMSE scores 24-30 used an antidepressant, versus none of those with MMSE scores lower than 24 (OR 1.2; C.I. 1.07-1.39).

Concerning physical health problems (chronic physical diseases and functional limitations) small differences in antidepressant use were found in favor of the more healthy respondents, but these were not statistically significant (results not shown).

Benzodiazepine use.

Table 3 shows benzodiazepine use (anxiolytics only) in the depressed groups. In all groups benzodiazepine use was higher than the use of antidepressants.

Sex differences in benzodiazepine use in the full sample and in the major depressive disorder group were sizable but not statistically significant: odds ratios were 1.6 (C.I. 0.7 - 3.4) for the full sample and 4.3 (C.I. 0.5 - 36.7) for the MDD group (with women using more benzodiazepines). In the dysthymia group benzodiazepine use was low in females and nonexistent in males. In the subthreshold depression group no sex differences were found.

Table 3. benzodiazepine use (BD use) in the depressed groups

	All			**males**			**females**		
	n	**BD**	**%BD**	**n**	**BD**	**%BD**	**n**	**BD**	**%BD**
SUBTHR	247	22	8.9%	99	9	9.1%	148	13	8.8%
DYSTH	25	2	8.0%	7	0	0%	18	2	11.1%
MDD	55	13	23.6%	12	1	8.3%	43	12	27.9%
TOTAL	327	37	11.3%	118	10	8.5 %	209	27	12.9%

DISCUSSION

As was expected, only a small minority of those depressed was using antidepressant medication, and in this group only 25-45 % had a therapeutic dosage.

The majority of depressed respondents had a subthreshold depression (75.5%), in which the necessity of using pharmacotherapy is not well established.

In the major depressive disorder group, only 16.4% used an antidepressant. In our sample we used 6 months prevalence, to exclude a very short duration of depressive complaints as a cause of not (yet) using medication. It is generally accepted that major depressive disorder is an indication for treatment, either pharmacologic or psychotherapeutic or both. There is clinical evidence that cognitive-behavioral therapy (CBT) and interpersonal therapy (IPT) are effective in older adults with MDD (Koder 1998; Miller, Cornes et al. 2001), but these forms of treatment are not well accessible, particularly in primary care in the Netherlands. We do not have information about psychotherapeutic treatment in our sample, but it is not to be expected that in the MDD group, respondents not using an antidepressant, all receive psychotherapy, considering the very small proportion having contact with a psychiatrist or mental health care center. So, in this seriously depressed group there is probably severe undertreatment. Lack of recognition of the depression, both by the physician as by the patiënt, may be an important factor in this undertreatment.

The fact that higher CES-D-scores were associated with more antidepressant use indicates that the recognition of the depression improves with severity.

Although women are twice as likely to be depressed as men, we did not find sex differences in antidepressant use.

There was a trend for an inverse association between rising age and antidepressant use. Physical problems did not seem to play a role in the use of antidepressants. In the major depressive disorder group, cognitive impairment (MMSE-score <23) was associated with low antidepressant use. A possible explanation is the diagnostic difficulty in this group: attention of physicians (and patients) may be focused on the cognitive problems, thereby overlooking the affective problems. Moreover, the presence of cognitive impairment (as a possible indication of dementia), may be considered a reason to refrain from treatment of the depression. In the cognitively impaired subsample, two respondents had an MMSE-score <14, so in most respondents only mild cognitive impairment was found, which is not a reason to renounce treatment.

In the depressed group benzodiazepine use was about twice as likely as antidepressant use. Anxiety symptoms, nervousness and sleep disturbances can cause difficulties in recognizing a depression. Probably persistent complaints about vague physical symptoms, or general feelings of distress, are looked upon as 'nervousness'. This can lead to the prescription of benzodiazepines instead of antidepressants. Benzodiazepines can relieve anxiety symptoms, nervousness and sleep disturbances, but can also have a depressing effect or lead to addiction, particularly when the depression (and thereby the benzodiazepine use) lasts longer. Our findings of sex differences in benzodiazepine use (females using more benzodiazepines) corresponds with the literature (van der Waals, Mohrs et al. 1993).

Limitations

Even in this large population-based study, numbers available for pertinent analyses were limited. The proportion of depressed respondents using an antidepressant or a benzodiazepine was very small, thereby impeding further statistical analyses of the role of age or physical problems, or the association with anxiety complaints. Inherent to the lower prevalence of depression in males, the number of men in the MDD group was too small for investigation of the role of sex in medication use.

Another problem is, that the data used are 10 years old, and it is possible that the situation has changed in these past 10 years. However, recent studies suggest that although prescription of antidepressants increases, it is still rather low (Wilson, Copeland et al. 1999).

A third problem is that only respondents with depressive complaints at the time of the interview were identified. Respondents who had been depressed, but received adequate treatment, were not included. Investigation of the 2600 non-depressed respondents of LASA baseline showed that 24 (1%) received an antidepressant. However, only 10 of them had a dosage considered to be adequate for treating depression. Compared with the 327 depressed respondents, and the 55 with MDD, this was only a small group.

Conclusions

The level of pharmacological treatment of depression in this sample of older people in the Netherlands was very low, also in the group with a serious, longer lasting, depressive disorder according to DSM-III-criteria, and particularly in the cognitively impaired. Moreover, if antidepressants were used, the dosage often was too low. A somewhat higher proportion used benzodiazepines, partly in combination with an antidepressant. However, benzodiazepines are not considered to be adequate treatment in major depressive disorder.

In this sample of older people with depression considerable undertreatment was found, which may have serious consequences for the patient.

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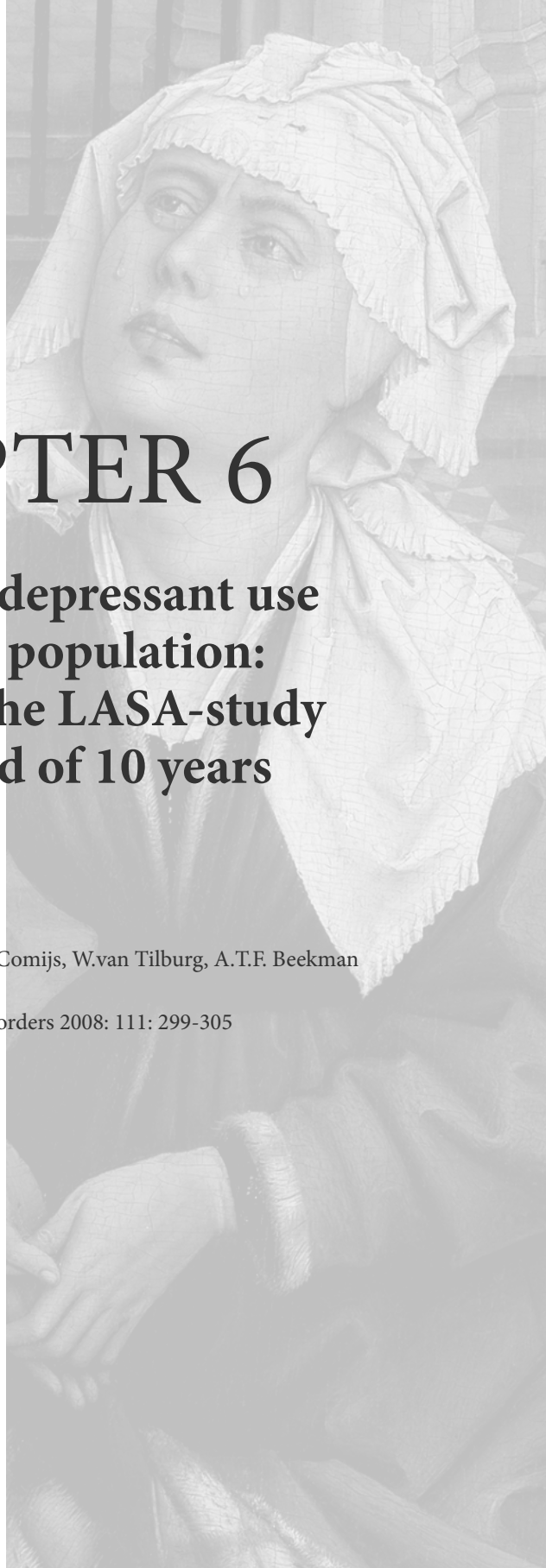

CHAPTER 6

Trends in antidepressant use in the older population: Results from the LASA-study over a period of 10 years

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Journal of Affective Disorders 2008: 111: 299-305

ABSTRACT

Background

In the past fifteen years, antidepressant use in adults has increased, mainly due to a rise in SSRI-use. The question is if this is true for older adults as well.

Methods

Data from the Longitudinal Aging Study Amsterdam were used to investigate trends in antidepressant use from 1992 through 2002 in a population-based sample aged 65-85 years.

Results

Antidepressant use increased from 2% to 6%. In the group with major depressive disorder, treatment with antidepressants showed an increase from 15% to 30%. This increase was larger in the older old than in the younger old. Also, the increase was mainly due to a rise in SSRI-use. Daily TCA-dosages often were too low; dosages of the other antidepressants seemed to be sufficient. However, rates of depression remained stable, in the treated as well as in the untreated group.

Limitations

non-response was associated with depression, the indication for prescription of antidepressants was not known, and serum concentrations of antidepressants were not available.

Conclusions

Antidepressant use in older people increased over the past fifteen years, mainly due to a rise in SSRI use. Daily dosages of antidepressants had become more adequate. Still only a minority of the more severely depressed used antidepressants.

INTRODUCTION

Depression is an important disorder in later life (Copeland, Davidson et al. 1992; Blazer, Kessler et al. 1994; Beekman, Deeg et al. 1995). Biological treatment and psychotherapy appear to be effective in older people (Hinrichsen 1992; Reynolds 1994; Schneider, Reynolds et al. 1994; Little, Reynolds et al. 1998; Miller, Cornes et al. 2001). However, several studies show undertreatment, varying from no treatment at all to non-therapeutic dosages of antidepressants or too early discontinuation of medication (Copeland, Davidson et al. 1992; Katon, von Korff et al. 1992; Blanchard, Waterreus et al. 1994; Koenig, George et al. 1997; Cole, Bellavance et al. 1999; Wilson, Copeland et al. 1999; Sonnenberg, Beekman et al. 2003). Undertreatment was found particularly in the oldest old, women, the chronically ill and people with cognitive impairment (Streim, Oslin et al. 2000; Sonnenberg, Beekman et al. 2003; Stek, Gussekloo et al. 2004).

In the past 15 years, the high rates of depression and their serious consequences for physical, psychological and social well-being in older adults, are better appreciated. The introduction of newer antidepressants, which are safer and have less serious side effects, has made pharmacological treatment less complicated. In younger adults, data have shown a huge increase in the prescription of antidepressants, especially SSRIs, also in primary health care (Donoghue, Tylee et al. 1996; van Marwijk, Bijl et al. 2001; Brugha, Bebbington et al. 2004). Such data are not available for older adults.

This study investigates time-trends in antidepressant use in an older, population-based sample over a period of ten years. Our hypotheses were that (i) antidepressant use in older people increased; (ii) this increase was due to an increase in SSRI-use, and (iii) sufficient dosages of the antidepressant were more often used.

In addition, we studied associations of antidepressant use with factors that are known to hamper the diagnosis and treatment of depression: older age, female sex, cognitive impairment, co-occurrent physical illness and functional limitations, and we investigated whether trends in antidepressant use differed across subgroups according to these factors.

METHODS

Sampling and procedures

Data were derived from the Longitudinal Aging Study Amsterdam (LASA), a longitudinal, interdisciplinary study on the predictors and consequences of changes in autonomy and well being in the aging population (Deeg and Westendorp-de Seriere 1994). Sampling procedures and characteristics of the sample have been described in detail in previous publications (Beekman, Deeg et al. 1995; Beekman, Geerlings et al. 2002; Deeg, van Tilburg et al. 2002). In short, the LASA-cohort is based on a representative sample of older adults between the ages of 55 and 85, stratified for age, sex and expected mortality five years into the study. It was drawn from the population registers of 11 municipalities in three regions of the Netherlands.

Data-collection started in 1992-1993 (T1), followed by data collection cycles every three years: in 1995-1996 (T2), 1998-1999 (T3), and 2001-2002 (T4). Trained interviewers using the same procedures and instruments interviewed respondents at home. All interviews were tape-recorded.

The number of participants at T1, T2, T3 and T4 were 3107, 2545, 2076 and 1691, respectively. Attrition between T1 and T4 was mainly due to mortality: percentages of people who died before approach were 13.4% between T1 and T2, 13.5% between T2 and T3, and 13.9% between T3 and T4. Other reasons for attrition were refusal (2.9%, 2.8% and 3.0% at T2, T3 and T4, respectively), frailty (1.2%, 1.7% and 1.5% at T2, T3 and T4, respectively), and failure to contact (0.6%, 0.5% and 0.1% at T2, T3 and T4, respectively). At all three follow-up cycles, attrition was related to older age and male sex, and to physical disease and cognitive impairment at the preceding cycle. Attrition at T2 was related to a low level of education, and to the presence of depression at T1, but these associations were not found at T3 or T4.

To address our research questions on analysis of time trends, sub-samples of equal ages (65-85 years) were selected at each cycle resulting in 2170, 1515, 1397 and 1222 participants at T1, T2, T3 and T4, respectively. Due to item-non-response the numbers of respondents available in these sub-samples were 1847, 1294, 1099 and 1119 at T1, T2, T3 and T4, respectively. These four sub-samples are referred to as study-samples.

Measures

Depression

Depressive symptoms were measured with the Center for Epidemiologic Studies Depression scale (CES-D), a 20-item self-report scale developed for use in the community (Radloff 1977; Radloff and Teri 1986). The CES-D has good psychometric properties in older community samples (Beekman, Deeg et al. 1997). There is minimal overlap with physical illness (Berkman, Berkman et al. 1986). Scores range from 0 to 60. Respondents scoring 16 or higher are considered to have a clinically relevant level of symptoms. Using this cut-off point the CES-D has very good criterion validity for major depressive disorder with a sensitivity of 100% and a specificity of 88% (Beekman, Deeg et al. 1997).

At T1, all subjects scoring above the cut-off score on the CES-D were approached for an additional, diagnostic interview, scheduled 2 to 8 weeks after the CES-D interview. In these subjects DSM-III diagnoses of major depressive disorder (6-month prevalence) were established using the Diagnostic Interview Schedule (DIS) (Robins, Helzer et al. 1981). From T2 to T4, the DIS was performed in the respondents who scored above the CES-D cut-off point at the preceding cycles, and in those newly depressed according to CES-D-scores. This two-stage design has been described in detail elsewhere (Beekman, Deeg et al. 1997; Penninx, Beekman et al. 2001; Beekman, Geerlings et al. 2002).

With these data on depressive symptoms and depressive disorder, three subgroups were distinguished at all four measurements: no depression (CESD-score < 16), subthreshold depression (CESD-score ³ 16 but no major depressive disorder) and major depressive disorder (as measured with the DIS).

Pharmacological treatment

Pharmacological treatment was assessed by recording the medication of the participants directly from the containers in the home of the respondents. The anatomical-therapeutical-chemical coding and categorization system for medication (Pahor, Chrischilles et al. 1994) was used to classify antidepressants. Antidepressants were subdivided in four categories: tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), lithium, and others (reversible MAO-A-inhibitors, atypical antidepressants). The daily dosage of antidepressant use was scored in four categories: not known, not therapeutic, probably therapeutic, and therapeutic.

Covariates

Age was used as a continuous variable (years) and in two age groups: 65-74 and 75-84 years. Cognitive impairment was measured with the Mini-Mental Status Examination (MMSE) using a cut-off score of 23 (Folstein, Folstein et al. 1975). Physical health was assessed using self-reports on chronic physical diseases, cross-checked with the GP's of the participants (Kriegsman, Penninx et al. 1996). Functional limitations were measured with self-reports on several activities of daily functioning, previously validated in the Netherlands (Van Sonsbeek 1988) (Kriegsman, Deeg et al. 1997).

Data analyses

To address our first research question, antidepressant use at T1 through T4 was calculated in the full study-samples and for the depressed and non-depressed subgroups separately.

In order to investigate time-trends, i.e. changes over time in antidepressant use, the data had to be made suitable for comparing the four cycles. First, prevalence data were weighted by age and sex, in order to reach a similar distribution of age and sex in the four study-samples, with the T4 sample used as the reference. The proportions of the four categories of antidepressants (TCAs, SSRIs, lithium and others) used at T1 through T4 were compared with each other.

Trends on daily doses of the antidepressants used were investigated by comparing the proportions of the four categories of dosage at T1 through T4.

Second, the factor 'time' was brought into the four study-samples as a covariate by adding the variable 'cycle number'. Changes over time were tested by assessing the association between antidepressant use and cycle number after pooling the four study-samples into one data file. In this file, logistic regression analyses were performed, with antidepressant use as the dependent variable and cycle number as the independent variable with T1 being the reference category, and independent covariates, and with p £ 0.05 as the criterion.

Because the sample size of the subgroup with major depressive disorder was relatively small, we calculated the power of this subgroup.

To address our second research question, the investigation of changes over time in the association between antidepressant use and the covariates, logistic regression analyses were performed in the full study-sample and in the depressed and non-depressed subgroups,

with antidepressant use as the dependent variable, and cycle number as a categorical covariate indicating time. To investigate whether trends over time differed across subgroups according to the covariates, interaction between cycle number and these covariates was investigated with logistic regression analyses, with p £ 0.05 as the criterion. When an interaction with time was found, logistic regression models were repeated for the separate strata of the covariate.

RESULTS

Table 1 shows demographic and health-related characteristics of the respondents participating in the four cycles, weighted for age and sex. 53.0% of the respondents belonged to the younger age group (65-74 years), and 52.3% were women. The proportion of respondents who were depressed remained rather stable over ten years. Impaired cognitive functioning showed a decrease. The presence of chronic physical illness and physical limitations increased.

Table 1. Characteristics of the study-sample (weighted for age and sex)

Period	**T1 ('92-'93) (n = 1847)**		**T2 ('95-'96) (n = 1294)**		**T3 ('98-'99) (n =1099)**		**T4 (2001-2002) (n = 1119)**	
Characteristic	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Depression:								
Not depressed	1568	84.9%	1097	84.8%	893	80.3%	955	85.3%
Depressed	279	15.1%	197	15.2%	216	19.7%	164	14.7%
- subthreshold depression	239	12.9%	159	12.3%	174	15.8%	141	12.6%
- major depressive disorder	40	2.2%	38	2.9%	42	3.8%	23	2.1%
Cognitive functioning								
Not impaired (MMSE ≥ 24)	1619	87.9 %	1157	89.6%	1001	91.2%	1049	93.7%
Impaired (MMSE < 24)	222	12.1 %	135	10.4 %	96	8.8 %	70	6.3 %
Chronic physical illness								
None	543	29.4%	209	16.2%	141	12.8%	162	14.5%
One or more	1301	70.6%	1085	83.8%	958	87.2%	957	85.5%
Physical limitations								
None	922	50.6%	608	47.6%	458	42.3%	499	45.0%
One or more	899	49.4%	668	52.4%	626	57.7%	609	55.0%

Antidepressant use

An increase of antidepressant use was found, particularly in the depressed subgroups (table 2). The increase in antidepressant use over time was statistically significant at T3 (OR=1.99; CI=1.28-3.11) and T4 (OR=2.72; CI=1.79-4.14) compared to T1. In the major depressive disorder subgroup, antidepressant use showed an increase from 15% to 30%, but no statistical significance was reached, probably due to the small numbers for antidepressant use in this subgroup (OR=2.48; CI=0.72-8.58). The power to detect change in this subgroup was 0.74, which is moderate. Neither the treated nor the untreated group showed a significant change in rates of depression (table 3).

Table 2. Antidepressant use and depression groups in the four cycles (weighted for age and sex)

Period	**T1**		**T2**		**T3**		**T4**	
	N	%	N	%	N	%	N	%
Antidepressant use in the full study-sample	(n = 1847) 37	2.0%	(n = 1294) 31	2.4%	(n = 1099) 43	3.9%	(n = 1119) 59	5.3%
Antidepressant use in the non-depressed subgroup	(n = 1568) 24	1.5%	(n = 1097) 24	2.2%	(n = 883) 22	2.5%	(n = 955) 35	3.7%
Antidepressant use in subthreshold depression subgroup	(n = 239) 7	2.9%	(n = 159) 5	3.1%	(n = 174) 12	6.9%	(n = 141) 17	12.1 %
Antidepressant use in depressive disorder subgroup	(n = 40) 6	15.0%	(n = 38) 2	5.3%	(n = 42) 9	21.4%	(n = 23) 7	30.4%

TCA-use showed a relative decrease from 68% of total antidepressant use at T1 to 37% at T4. SSRI-use showed a relative increase from 13 % of total antidepressant use at T1 to 49% at T4; lithium-use a relative decrease from 13% to 8%. The use of atypical antidepressants showed some variation in this period, but overall change was small (from 5% to 7%).

The rise in total antidepressant use was mainly due to the rise in SSRI-use (from 0.2% at T1 to 2.6% at T4). Even TCA-use still showed a moderate increase from 1.3% to 1.8%.

At T1, 42% of those using an antidepressant had a daily dose that was considered to be

therapeutic for depression. In the depressed subgroup this was only 17%; another 25% had a daily dose that may be therapeutic. At T2, 59% of those with an antidepressant had a sufficient dose, and 75% of the depressed. At T3, this was 72% and 79% respectively, and at T4 rather similar rates were found: 70% and 75% respectively.

Table 3. Depression and treatment groups in the four cycles (weighted for age and sex)

Period	**T1**		**T2**		**T3**		**T4**	
	N	%	N	%	N	**%**	N	%
Depression in the non-treated subgroup:	(n = 1810)		(n = 1263)		(n = 1056)		(n = 1060)	
- depressive disorder	34	1.9%	36	2.9%	33	3.1%	16	1.5%
- subthreshold dep	232	12.8%	154	12.2%	162	15.3%	124	11.7%
- no depression	1544	85.3%	1073	85.0%	861	81.6%	920	86.8%
Depression in the treated subgroup:	(n = 37)		(n = 31)		(n = 43)		(n = 59)	
- depressive disorder	6	16.2%	2	6.5%	9	20.9%	7	11.9 %
- subthreshold dep	7	18.9%	3	16.1%	12	27.9%	17	28.8%
- no depression	24	64.9%	24	77.4%	22	51.2%	25	59.3%

Risk factors

Multivariate analyses in the pooled data-file showed a statistically significant association of antidepressant use with depression (OR=2.51; CI=1.79-3.54), functional limitations (OR=1.91; CI=1.30-2.80) and cognitive impairment (OR=1.76; CI=1.14-2.72). No association was found for sex, age and chronic physical illness.

In the non-depressed subgroups, antidepressant use was associated with cognitive impairment (OR=1.94; CI=1.09-3.44), functional limitations (OR=2.22; CI=1.42-3.47) and chronic physical illness (OR=2.26; CI=1.12-4.57). In the subthreshold depression subgroup, antidepressant use was associated only with cognitive impairment (OR=2.61; CI=1.25-5.46). In the major depressive disorder subgroup no significant association was found with any of these factors.

A statistically significant interaction for antidepressant use was found between age and cycle number (OR=1.35; CI=1.03-1.77). Therefore, multivariate analyses were repeated for

the two age strata. In these analyses, a statistically significant association of antidepressant use with cycle number was found in the older age group (75-85 years) with increasing antidepressant use from T1 to T3 (OR=2.78; CI=1.45-5.30) and T4 (OR=4.19; CI=2.24-7.83). No interactions between cycle number and sex, cognitive functioning, functional limitations or chronic physical illness were found.

DISCUSSION

In this study, we found that antidepressant use in an older Dutch population-based sample increased from 2% to 6% in the period from 1992 through 2002. This corresponds with the increase that is found in younger adults in this period (van Marwijk, Bijl et al. 2001; Brugha, Bebbington et al. 2004).

The largest increase was found in the subgroup with subthreshold depression, with a rise from 2% to 12%. In the subgroup with a major depressive disorder, treatment with antidepressants was doubled. However, even in 2002 only 30% of those with major depressive disorder used antidepressants, which is still a minority.

The increase in antidepressant use was mainly due to a sharp rise in SSRI-use, whereas TCA-use and use of other antidepressants remained rather stable.

The rise of antidepressant use in the non-depressed and subthreshold depression group may be an indication that more people with depression are being treated well, with treatment leading to amelioration or remission of symptoms. However, given the huge increase in antidepressant use that was found, it is not likely that this is the only explanation. Besides, depression rates decreased neither in the treated, nor in the untreated group. The rise in antidepressant use may be due to prescription for other indications than depression. TCAs are also prescribed for chronic pain management. SSRIs are indicated for the treatment of several anxiety disorders. Moreover, SSRIs are prescribed more easily because they are relatively harmless and have simple dosing schemes, compared to TCAs. It has been suggested that SSRIs may be prescribed more often unnecessarily or with a questionable indication, e.g. in the case of depression not fulfilling the criteria for major depression (Rosholm, Gram et al. 1995; De Neeling 2000). Since respondents in this study were not asked about the indication for their antidepressant use, or why they continued it without having (serious) depressive complaints, it is not possible to resolve this question.

An improvement of the prescribed daily dosages was found, shown by the increasing group with probably therapeutic dosages for lithium, SSRIs and the category other antidepressants. In the TCA-group more than half used very low dosages (e.g. 10 or 20 mg daily) throughout the study period. An explanation for this finding may be the more complicated dosing schemes of the TCAs, the more serious side effects like cardiac rhythm disturbances and orthostatic hypotension, and the risk of lethal intoxication in case of suicidal behaviour. In the Netherlands, a change from TCA-use to SSRI-use in primary mental health care was observed soon after the introduction of the SSRIs, despite TCAs being the first choice in the Dutch guidelines for primary care at that time (Van Marwijk, Grundmeijer et al. 1994).

People with major depressive disorder had the highest rate of antidepressant use (30%). Nevertheless, this rate still was low. Difficulties in diagnosing depression in older people may play a role in this undertreatment (Lindesay, Briggs et al. 1989; Copeland, Davidson et al. 1992; Blazer, Kessler et al. 1994; Tannock and Katona 1995; Streim, Oslin et al. 2000). Of the factors known to be a risk factor for depression in older people, but also to hamper diagnosis and treatment of this depression, the presence of mild cognitive impairment, chronic physical illness and functional limitations were associated with antidepressant use. Overall, these were positive associations, with a higher antidepressant use in these groups. In the major depressive disorder group with cognitive problems antidepressant use was almost non-existent, but no statistical significance was reached here.

It was remarkable that no association was found between antidepressant use and age or sex. Particularly older age is supposed to be a risk factor for undertreatment, due to low expectations of the effectiveness of treatment in older depressed persons for both medication and psychotherapy (Reynolds, Frank et al. 1994; Reynolds, Frank et al. 1996; Cole, Bellavance et al. 1999). In the older group an increase of antidepressant use was found. This may be an indication that treatment of depression in the older-old is getting more attention, and that this group has taken advantage of the rise in SSRI-use.

There are some limitations of this study. First, attrition from the sample between T1 and T2 was associated with depression. Therefore it is presumable that in this study antidepressant use is underestimated when compared to the population. Second, as discussed above, there were no data on the indication for the use of the antidepressants. Finally, for reviewing the therapeutic adequacy of the antidepressants, data on the dosages of the antidepressants

were available, but data on serum concentrations were not. Particularly in the case of the TCAs this may be a problem, because there are great individual differences in the doses that are necessary to reach adequate serum concentrations. However, it is very unlikely that a dosage of 25 mgs or less is effective in the treatment of depression.

In conclusion, our most important finding was that in this older Dutch population-based sample, antidepressant use increased from 1992 through 2002, particularly in the older-old. However, still only a minority of the more severely depressed older people used antidepressants in an adequate dose.

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CHAPTER 7

Ten-year trends in benzodiazepine use in the Dutch population

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Social Psychiatry and Psychiatric Epidemiology 2012: 47: 293-301

ABSTRACT

Background

In the past decades knowledge on adequate treatment of affective disorders and awareness of the negative consequences of long-term benzodiazepine use increased. Therefore, a decrease in benzodiazepine use is expected, particularly in prolonged use. The aim of this study was to assess time trends in benzodiazepine use.

Methods and material

Data from the Longitudinal Aging Study Amsterdam were used to investigate trends in benzodiazepine use between 1992 and 2002 in two population-based samples aged 55-64 years. Differences between the two samples with respect to benzodiazepine use and to sociodemographic, physical health and mental health characteristics were described and tested with chi-square tests, t-tests for independent samples and logistic regression analyses.

Results

Benzodiazepine use remained stable over 10 years, with 7.8% in LASA-1 (n = 874) and 7.9% in LASA-2 (n = 919) with a persisting preponderance in women and in people with low education, low income, chronic physical diseases, functional limitations, cognitive impairment, depression, anxiety complaints, sleep problems and when using antidepressants. Long-term use remained high with 70% in 1992 and 80 % in 2002 of total benzodiazepine use.

Conclusion

In the Dutch population aged 55-64, overall benzodiazepine use remained stable from 1992 to 2002, with a high proportion of long-term users, despite the effort to reduce benzodiazepine use and the renewal of the guidelines. More effort should be made to decrease prolonged benzodiazepine use in this middle-aged group, because of the increasing risks with aging.

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INTRODUCTION

Benzodiazepines are widely used in the treatment of anxiety complaints, nervousness and sleep problems (Curran 1991; Barbee 1993; King 1994; Kirby, Denihan et al. 1999; Jorm, Grayson et al. 2000; Zandstra, Furer et al. 2002). Although people may benefit from their anxiolytic and hypnotic effects, when used for a longer period (more than two months) benzodiazepine use may lead to addiction problems, with withdrawal symptoms, diminishing effect and difficulty in discontinuing treatment (Voshaar, Couvee et al. 2006). Particularly in later life, benzodiazepines have serious adverse effects, such as an increased risk of mobility and ADL problems (Gray, Penninx et al. 2003; Gray, LaCroix et al. 2006), falling (Sorock and Shimkin 1988; Cumming and Le Couteur 2003; Pariente, Dartigues et al. 2008; van der Hooft, Schoofs et al. 2008) and a negative effect on cognitive functioning (Hanlon, Horner et al. 1998; Hogan, Maxwell et al. 2003; Pat McAndrews, Weiss et al. 2003; Barker, Greenwood et al. 2004; Stewart 2005; Bierman, Comijs et al. 2007). They can cause sedation and impairment of driving skills (Madhusoodanan and Bogunovic 2004). Mental and physical health and cognitive performance improve after discontinuation of benzodiazepines, particularly sleeping pills (Ashton 2005). Despite these known side-effects, benzodiazepines are widely used, also by middle-aged and older people and often for long periods of time (Curran 1991; Barbee 1993; Balestrieri, Bortolomasi et al. 1997; Forsell and Winblad 1997; Kirby, Denihan et al. 1999; Jorm, Grayson et al. 2000; Lagnaoui, Depont et al. 2004; Luijendijk, Tiemeier et al. 2008). Although dose escalation is rare in older people (Soumerai, Simoni-Wastila et al. 2003; Cook, Marshall et al. 2007), discontinuation of benzodiazepine use is found to be more difficult with aging, particularly after the age of 45 (Dunbar, Perera et al. 1989; Cans and Rotily 1991; Cook, Biyanova et al. 2007).

In the past decades depression and anxiety disorders have gained a lot of attention, leading to increasing emphasis on the importance of adequate treatment of these disorders. The newer generation of antidepressants, the selective serotonine reuptake inhibitors (SSRI's), which are used in the treatment of depression as well as anxiety disorders, have become very popular and their use has shown a huge increase in the past decades (van Marwijk, Bijl et al. 2001; Brugha, Bebbington et al. 2004). Also, the increasing knowledge of the impact of side effects and addiction problems of benzodiazepines has lead to the recommendation of short-term prescription and discontinuing use when possible, particularly in older people, with a preference for the short working benzodiazepines without pharmacologically active metabolites (Hogan, Maxwell et al. 2003).

In the Dutch guidelines on pharmacological treatment of anxiety disorders serotonergic antidepressants are advised for pharmacological treatment. Benzodiazepines are recommended for short-term treatment only, in anxiety disorders as well as in mood disorders, with an exception of anxiety disorders that do no respond to two different SSRI's (Neomagus, Terluin et al.1997; van Balkom, van Dyck et al. 1998). Furthermore, in these years several types of psychotherapy have proven to be effective as well in anxiety and sleep disorders, e.g. exposure with response prevention and cognitive behaviour therapy, and they can be applied with or without pharmacotherapy (van Balkom, van Dyck et al. 1998; Riemann and Perlis 2009). Thus, it might be expected that benzodiazepine use, and particularly long-term use, has decreased in the past years due to improved clinical practice. Another development that may have led to a decrease in benzodiazepine use is the increase of interest in and knowledge on physical and mental health issues in the general population in the past decades through the mass media and the more open communication. This has led to an increasing awareness of positive and negative consequences of drug use and an enhanced participation of patients in the process of medical decision-making.

In the literature, prevalence rates of benzodiazepine vary between 2 and 17%, due to the variety in definitions of benzodiazepine use and observation period (Zandstra, Furer et al. 2002). Conclusions on whether benzodiazepine use is stable in time are therefore not easily made. Consistent findings are that benzodiazepine use in women stays twice as high as in men, and that benzodiazepine use is higher in older people with a preponderance of long-term use (Zandstra, Furer et al. 2002).

Objectives

Our hypothesis is that in the past decades the development of special treatment for anxiety disorders, the introduction of SSRI's and the awareness of the addiction problems and the side effects of benzodiazepines have led to a decrease of benzodiazepine use, with a more adequate application and shorter use of benzodiazepines. We will investigate this in two population-based samples taking age, sex, income, education, physical problems, cognition, depression, anxiety, sleep problems, antidepressant use and alcohol use, into consideration. We chose this middle-aged group (55-64 years) because of the increasing risks of long-term benzodiazepine use when people grow older.

METHODS

Sampling and procedures

Data were derived from the Longitudinal Aging Study Amsterdam (LASA), a longitudinal, interdisciplinary study on the predictors and consequences of changes in autonomy and well-being in the aging population (Deeg and Westenberg-de Seriere 1994). Baseline sampling procedures and characteristics of the sample have been described in detail in previous publications (Beekman, Deeg et al. 1995; Beekman, Geerlings et al. 2002; Deeg, van Tilburg et al. 2002). In short, the LASA sample is based on a representative random sample of 3107 older adults between the ages of 55 and 85, stratified for age, sex and expected mortality five years into the study. The sample was drawn from the population registers of 11 municipalities in three regions of the Netherlands. Non-response in the first LASA-cycle was related to age, but not to gender. Data-collection in LASA started in 1992-1993 (LASA-baseline) and participants were questioned every 3 years ever since. In 2002/2003 a new population sample was drawn, called LASA-2, by using the same sampling procedures to LASA-1. LASA-2 consisted of 1002 respondents, with ages ranging from 55 to 64.

To address our research question, shifts in benzodiazepine use in ten years, respondents of equal ages (55-64 years) from both samples were selected, resulting in 966 (LASA-1) and 1002 (LASA-2) participants. Due to missing information on benzodiazepine use, samples of n = 874 (LASA-1) and 919 (LASA-2) were available for the analyses. In both samples this selection was not related to age, gender, or the other covariates.

All interviews were conducted in the homes of the respondents, by specially trained and intensively supervised interviewers. Informed consent was obtained from each respondent, according to the prevailing legal requirements. The study was approved by the Medical Ethical Committee of the VU University Medical Centre.

Measures

Use of benzodiazepines

Use of prescribed drugs was assessed in LASA-1 and LASA-2 by recording the medication from the drug containers in the home of the respondents, and the duration of use was registrated. The anatomical-therapeutical-chemical (ATC) coding and categorization system for drug data coding (Pahor, Chrischilles et al. 1994) was used to classify all

medication. Benzodiazepines were categorised as tranquillising agents (anxiolytics) or sleeping pills (hypnotics). Separate nominal variables were defined, indicating the use of anxiolytic drugs or hypnotic drugs (coded as 'yes' or 'no').

Duration of use was divided in 4 categories: short-term (< 1 month), moderate (1 month – 1 year), long-term (>1 year) and irregular (sometimes) use. When a respondent used more than one benzodiazepine, the longest use was counted.

The elimination time and the presence of pharmacologically active metabolites of the benzodiazepines were evaluated. The elimination time was considered long when half-life was > 20 hours. Presence (yes) or absence (no) of metabolites was established.

Covariates

Sex was investigated as a covariate, because of the preponderance of women in benzodiazepine use (Wells, Kamberg et al. 1985; Swartz, Landerman et al. 1991; van der Waals, Mohrs et al. 1993; Neutel 2005; Kassam and Patten 2006; Fortin, Preville et al. 2007), and in the prevalences of depression and anxiety disorders (Weissman, Leaf et al. 1984; Kessler, McGonagle et al. 1993).

Because *socio-economic status* is known to be associated with health status and health behavior, and with benzodiazepine use (Wells, Kamberg et al. 1985; Swartz, Landerman et al. 1991; Kassam and Patten 2006), the level of education and the level of income were included as covariates.

The *level of education* was classified in three levels: low education (elementary school not completed, elementary education), medium education (lower vocational, general intermediate, intermediate vocational, general secondary education), and high education (higher vocational, college and university education).

Income was classified in three levels: low income (< 1000 Euros per month), intermediate income (1000-3000 Euros per month) and high income (more than 3000 Euros per month). Income in LASA-1 was corrected for inflation of 3% per year until 2002.

Impaired *physical health* is associated with depression and anxiety complaints. Therefore chronic diseases and functional limitations were included as independent variables.

Chronic diseases were assessed using specific questions on chronic non-specific lung disease, cardiac disease, peripheral atherosclerosis, stroke, diabetes mellitus, arthritis, malignant neoplasms, and a maximum of two other chronic diseases. The total number of diseases ranged from 0 to 9. These data were cross-checked with the General Practitioners of the participants. Accuracy of self-report was shown to be independent of cognitive impairment, level of depressive symptoms and anxiety symptoms (Kriegsman, Penninx et al. 1996) .

Functional limitations were measured with a questionnaire on difficulty experienced with several activities (walking up and down stairs, using public transportation and cutting own toenails). This questionnaire was validated in the Netherlands by Van Sonsbeek (van Sonsbeek 1988) and Kriegsman et al. (Kriegsman, Deeg et al. 1997).

Cognitive impairment might hamper recognition and treatment of affective disorders, but it can also be a side effect of benzodiazepine use. Cognitive impairment was measured with the Mini-Mental State Examination (MMSE), a frequently used screening instrument for global cognitive functioning. Scores range from 0 to 30 with higher scores indicating better cognitive performance. We used the cut-off score of 23, with scores ≤23 indicating cognitive impairment (Folstein, Folstein et al. 1975).

Excessive *alcohol consumption* may be an indication for addiction problems, but it can also be used as self-medication in the case of withdrawal symptoms in excessive benzodiazepine use. Alcohol consumption was assessed with a questionnaire developed for the Netherlands Health Interview Survey (CBS 1993) and classified according to the Garretsen Index of Present Alcohol Use (Garretsen 1983), into three categories (excessive/severe, moderate/light and non-drinker).

Depressive symptoms, anxiety symptoms and sleep problems, often the reason for benzodiazepine use, were measured with the Centre for Epidemiologic Studies Depression Scale (CES-D), a 20-item self-report scale developed for use in the community (Radloff 1977; Radloff and Teri 1986; Beekman, Deeg et al. 1997). The CES-D ranges from 0 to 60 with higher scores indicating more depressive symptoms. The dichotomous score based on the commonly used cut-off score of 16 was used (Berkman, Berkman et al. 1986) to indicate clinically relevant depressive symptoms. Although the CES-D was designed for the screening of depressive symptoms, it may also be used as a screener of anxiety

symptoms (Beekman, Deeg et al. 1997). We used the particular CES-D item about feelings of nervousness and tension (item number 10: feeling fearful) to measure *anxiety*. To investigate *sleep problems* we used CES-D item number 11 (sleep being restless). This item had a good correlation with a larger questionnaire in LASA on sleep problems and could therefore be used as an indicator of sleep problems.

Antidepressant use was measured in the same way as benzodiazepine use, i.e. based on information on the drug containers, provided by the respondents. A separate nominal variable was defined, indicating the use of antidepressant drugs, coded as 'yes' or 'no'.

Statistical analyses

Details of this procedure are described in another publication (Sonnenberg, Deeg et al. 2008). In order to investigate time trends, i.e. changes over time in benzodiazepine use, the data had to be made suitable for comparing the two cycles. Therefore, prevalence data were weighted by age and sex, in order to reach a similar distribution of age and sex in the two study samples, with LASA-1 as the reference. To investigate the differences in benzodiazepine use between LASA-1 and LASA-2, i.e. to make a comparison between the two samples possible, we pooled the data from both samples and added the factor 'time' by defining the variable 'sample number' (1 = LASA-1 and 2 = LASA-2). In this pooled data file, first, for descriptive purposes, the differences between LASA-1 and LASA-2 with respect to benzodiazepine use and all covariates were tested using chi-square tests. Likewise, the differences between LASA-1 and LASA-2 within the groups of benzodiazepine users with respect to the covariates were tested using chi-square tests. In the pooled sample, associations of benzodiazepine use with the separate covariates were investigated in bivariate analyses using chi-square tests. To investigate the association of time and the other covariates with benzodiazepine use in a multivariate model, logistic regression analyses were performed, with benzodiazepine use as the dependent variable, and with time and the other covariates entered stepwise into the model. To investigate effect modification of the covariates on time differences in benzodiazepine use, logistic regression analyses with interaction-terms of time with the covariates were performed. In the chi-square tests,and the logistic regression analyses, p-values < 0.05 were regarded as statistically significant.

RESULTS

An overview of the characteristics and the differences between LASA-1 and LASA-2 is shown in table 1. Benzodiazepine use showed no major difference between the two samples with 7.8% in LASA-1 and 7.9% in LASA-2 (p=0.90), nor did separate rates of tranquillising agents (3.7% and 4.8% resp., p=0.24) and sleeping pills (4.6% and 3.9% resp., p=0.49). In both samples the majority of the benzodiazepines was used for a long period. In LASA-1 26% was used during a month to a year, and 69% was used longer than one year. In LASA-2 these percentages were 15% and 80%. Use of short-working benzodiazepines without pharmacologically active metabolites increased from 56% in LASA-1 to 65% in LASA-2.

Table 1. Socio-demographic characteristics, physical and mental health and benzodiazepine use in LASA-1 and LASA-2.

	LASA-1 **N = 874**		**LASA-2** **N = 919**		*Sample differences*
	N	*%*	*N*	*%*	*P-value*
Education:					
Low	268	30.7 %	188	20.5 %	**p= 0.00**
Intermediate	479	54.8 %	532	57.9 %	
High	127	14.5 %	199	21.7 %	
Income: *					
Low	135	18.9 %	100	11.9 %	**p= 0.00**
Medium	370	51.7 %	365	43.5 %	
High	211	29.5 %	375	44.6 %	
Chronic diseases:					
None	310	35.5 %	243	26.4 %	**p= 0.00**
One or more	564	64.5 %	676	73.6 %	
Functional limitations (of #3):					
None	725	83.0 %	667	72.6 %	**p= 0.00**
One or more	149	17.0 %	252	27.4 %	
Cognitive impairment:					
No: MMSE > 23	848	97.0 %	888	96.6 %	p = 0.52
Yes: MMSE ≤ 23	26	3.0 %	31	3.4 %	

Table 1. Continued.

	LASA-1 N = 874		**LASA-2 N = 919**		*Sample differences*
	N	*%*	*N*	*%*	*P-value*
Depression:					
No	781	89.4 %	790	86.0 %	**p= 0.03**
Yes (CESD ≥ 16)	93	10.6 %	129	14.0 %	
Anxiety: being fearful					
No	785	89.8 %	803	87.4 %	p = 0.16
Sometimes - often	89	10.2 %	116	12.6 %	
Sleep problems:					
Never / some of the time	753	86.2 %	758	82.5 %	**p= 0.03**
Occasionally - often – always	121	13.8 %	161	17.5%	
Use of alcohol:					
Never	129	14.8 %	75	8.2 %	**p= 0.00**
Light – moderate	683	78.1 %	744	80.9 %	
(very) excessive	62	7.1 %	100	10.9 %	
Antidepressant users:					
No	861	98.5 %	883	96.1 %	**p= 0.00**
Yes	13	1.5 %	36	3.9 %	
Benzodiazepine users:					
All	68	7.8 %	73	7.9 %	p = 0.90
Anxiolytic users	32	3.7 %	44	4.8 %	p = 0.24
Hypnotic users	40	4.6 %	36	3.9 %	p = 0.49
Length of benzodiazepine use:**					
Short-term (< 1 month)	3	5.5 %	4	5.5 %	p = 0.34
Moderate (1 month – 1 year)	14	25.5 %	11	15.1 %	
Long-term (> 1 year)	38	69.1 %	58	79.5 %	
Long half-life and/or active metabolites of benzodiazepines:					
No	38	55.9 %	47	64.4 %	p = 0.30
Yes	30	44.1 %	26	35.6 %	

* in the questionnaire about income, respondents were able to choose the option 'wishes not to answer'; this resulted in 'no answer' in 158 respondents (18.1%) in LASA-1 and in 79 respondents (8.6%) in LASA-2. This category was left out of the analyses

**: in LASA-1 duration of benzodiazepine use was not known in 13 respondents (19.1%), leaving 55 out of 68 benzodiazepine users available for the analyses in length of benzodiazepine use

As a consequence of the weighing procedure, age and gender were equally distributed in the two samples. In LASA-1 47.9% were men and in LASA-2 47.2% were men, p=0.76. Mean age in LASA-1 was 59.7 years, and in LASA-2 this was 59.4 years.

The second sample was higher educated and had a higher income despite the inflation correction. Furthermore, respondents in LASA-2 reported more chronic diseases and functional limitations, and showed more depressive symptoms. They also reported more sleep problems. The presence of cognitive impairment and anxiety symptoms remained rather stable in the two samples. In LASA-2 more respondents used alcohol and there was also a rise in the amount of alcohol used. Furthermore, there was a remarkable increase of antidepressant use.

Table 2. Benzodiazepine use by socio-demographic and health measures in LASA-1 and LASA-2 and in the pooled sample (LASA 1+2)

	LASA-1 N = 874		**LASA-2 N = 919**		*Time differences for the subgroups*	**LASA 1+2 pooled sample N = 1793**		*Subgroup differences (in pooled sample)*
	Benzodiazepine users:		**Benzodiazepine users:**			**Benzodiazepine users**		
Subgroups:	*N*	*% in subgoup*	*N*	*% in subgroup*	*P-value*	*N*	*% in subgroup*	*P-value*
Sex:								
Men	21	5.0 %	14	3.2 %	p = 0.19	35	4.1%	**p = 0.00**
Women	47	10.3 %	59	12.2 %	p = 0.37	106	11.3%	
Education:								
Low	25	9.3 %	22	11.7 %	p = 0.41	47	10.3%	**p = 0.02**
Intermediate	34	7.1 %	44	8.3 %	p = 0.49	78	7.7%	
High	9	7.1 %	7	3.5 %	p = 0.15	16	4.9%	
Income:								
Low	16	11.9 %	15	15.0 %	p = 0.48	31	13.2%	**p = 0.00**
Medium	23	6.2 %	27	7.4 %	p = 0.53	50	6.8%	
High	15	7.1 %	22	5.9 %	p = 0.55	37	6.1%	
Chronic diseases:								
None	12	3.9 %	8	3.3 %	p = 0.72	20	3.6%	**p = 0.00**
One or more	56	9.9 %	65	9.6 %	p = 0.85	121	9.8%	
Cognitive impairment:								
No: MMSE > 23	63	7.4 %	67	7.5 %	p = 0.93	130	7.5%	**p = 0.00**
Yes: MMSE ≤ 23	5	19.2 %	6	19.4 %	p = 0.99	11	19.3%	

Table 2. Continued.

	LASA-1 N = 874		**LASA-2 N = 919**		*Time differences for the subgroups*	**LASA 1+2 pooled sample N = 1793**		*Subgroup differences (in pooled sample)*
	Benzodiazepine users:		**Benzodiazepine users:**			**Benzodiazepine users**		
Subgroups:	*N*	*% in subgoup*	*N*	*% in subgroup*	*P-value*	*N*	*% in subgroup*	*P-value*
Depression:								
No (CESD < 16)	47	6.0 %	42	5.3 %	p = 0.55	89	5.7%	**p = 0.00**
Yes (CESD ≥ 16)	21	22.6 %	31	24.0 %	p = 0.80	52	23.4%	
Anxiety: being fearful								
No	53	6.8 %	49	6.1 %	p = 0.60	102	6.4%	**p = 0.00**
Sometimes - often	15	16.9 %	24	20.7 %	p = 0.49	39	19.0%	
Sleep problems:								
Never - sometimes	47	6.2 %	36	4.7 %	p = 0.20	83	5.5%	**p = 0.00**
Occasionally – often – always	21	17.4 %	37	23.0 %	p = 0.25	58	20.6%	
Use of alcohol:								
Never	15	11.6 %	12	16.0 %	p = 0.37	27	13.2%	**p = 0.00**
Light – moderate	51	7.5 %	56	7.5 %	p = 0.97	107	7.5%	
(very) Excessive	2	3.2 %	5	5.0 %	p = 0.59	7	4.3%	
Antidepressant use:								
No	62	7.2 %	63	7.1 %	p = 0.96	125	7.2%	**p = 0.00**
Yes	6	46.2 %	10	27.8 %	p = 0.23	16	32.7%	

Table 2 shows time differences in benzodiazepine use in the socio-demographic and health subgroups and associations of benzodiazepine use with these subgroups in the pooled sample. Although an increase of benzodiazepine use was found in several subgroups (e.g. in women, in respondents with low education or low income, and in the case of depression, anxiety and sleep problems) and a decrease in other subgroups (e.g. men, high education, high income, and antidepressant users), these differences were not statistically significant, probably due to the small numbers in several subgroups.

In the pooled sample, benzodiazepine use was significantly higher in women, and in the respondents with chronic physical disease, functional limitations, cognitive impairment,

depression, anxiety, sleep problems and when using an antidepressant. Benzodiazepine use was lower in respondents with higher education, higher income and with higher alcohol use.

Table 3 shows the Odds Ratios for benzodiazepine use and time and the other covariates. The bivariate logistic regression analyses showed statistically significant associations of benzodiazepine use with all covariates, but not with time and age. In the multivariate regression analyses, controlling for all covariates including time, benzodiazepine use was found to be associated with female sex, and with the presence of one or more chronic diseases, depression, sleep problems and antidepressant use.

Table 3. Odds Ratios with 95% CI for benzodiazepine use and time, sociodemographic and health measures, unadjusted and adjusted for all co-variates, in the pooled sample.

	Benzodiazepine use in the pooled sample			
	unadjusted		***adjusted***	
	OR	***95% CI***	***OR***	***95% CI***
Time	1.02	0.73-1.44	0.80	0.54-1.18
Female sex	**2.97**	**2.00-4.41**	**2.31**	**1.50-3.57**
Older age group	1.09	0.77-1.54	1.00	0.69-1.45
Higher education	**0.69**	**0.53-0.90**	0.95	0.70-1.30
Higher income	**0.79**	**0.68-0.94**	0.99	0.82-1.20
One or more chronic diseases	**2.88**	**1.78-4.68**	**1.86**	**1.11-3.10**
One or more functional limitations	**2.41**	**1.69-3.46**	1.26	0.82-1.93
Cognitive impairment	**2.95**	**1.50-5.84**	1.70	0.77-3.80
Depression	**5.09**	**3.49-7.43**	**2.28**	**1.43-3.64**
Anxiety	**3.42**	**2.29-5.12**	1.38	0.86-2.24
Sleep problems	**4.46**	**3.10-6.41**	**2.29**	**1.50-3.50**
Use of alcohol	**0.54**	**0.37-0.78**	0.83	0.55-1.26
Antidepressant use	**6.28**	**3.36-11.72**	**3.71**	**1.83-7.52**

Investigation of the interaction between time and the independent variables did not show any statistically significant interaction (results not shown).

DISCUSSION

In the present study shifts in benzodiazepine use from 1992 to 2002 were investigated in a population-based sample aged 55-64 years.

We expected a decrease of benzodiazepine use due to enhanced knowledge of the effects of long-term benzodiazepine use and insight into adequate treatment of depression, anxiety and sleep problems. However, benzodiazepine use remained stable. Furthermore, long-term use remained high despite recommendations in the guidelines to keep treatment short. However, compared to the increase of antidepressant use in this period, the stability in benzodiazepine use may be considered a relatively positive finding. A trend in preference was found for short-working benzodiazepines without pharmacologically active metabolites, which is also a positive finding in this middle-aged group.

In our study, several socio-demographic characteristics and physical health and mental health factors that are known to be associated with benzodiazepine use showed differences in the two samples. We found a decrease in the prevalence of low income and low education, and an increase in the prevalence of physical health problems, depression, sleep problems, alcohol use and antidepressant use. However, the shifts in the presence of these characteristics and risk factors did not affect their associations with benzodiazepine use, nor did age or sex: all factors except time and age were associated with benzodiazepine use. This is in line with the literature (Luijendijk, Tiemeier et al. 2008). Being a woman, having one or more chronic diseases, depression, sleep problems and the use of antidepressants, remained associated with benzodiazepine use in the multivariate analyses and were considered to explain the association with the other risk factors.

In 2002, women and respondents with low education still used more benzodiazepines. Respondents with chronic physical disease and functional limitations still used more benzodiazepines. Although they may diminish feelings of distress and sleep problems, they can also cause sedation, muscle weakness and increase the risk of falling in this physically vulnerable group. In the respondents with cognitive impairment, benzodiazepines are often used successfully to reduce concomitant anxiety and sleep disturbances, but they may increase memory problems and reduce attention, alertness and mental speed. In the case of depression, anxiety and sleep problems, benzodiazepine use remained high, although it is recommended only for short-term use or for support in the first weeks of treatment with antidepressants or psychotherapy. Prolonged use of benzodiazepines may even worsen the

depressive symptoms (Dhondt, Derksen et al. 1999; van Vliet, van der Mast et al. 2009).

The combination of benzodiazepine use and the use of alcohol is important because of the possibility of excessive sedation and mood disturbances. In the alcohol users benzodiazepine use was lower than in the full sample, but some respondents combined alcohol with benzodiazepine, which may lead to important health problems e.g. a higher risk of falling, memory problems and traffic accidents, particularly when this group gets older.

Strenghts and limitations of the study

There are some limitations to this study. Access to two large population based samples with data concerning a wide variety of relevant variables makes LASA very well suited for an investigation of trends in benzodiazepine use. However, within specific subgroups, the numbers of respondents using benzodiazepines were small, which limits statistical analyses in subgroups. A second limitation of the present study is the use of self-reports. This may cause report bias, due to problems in the recall of information from the past (chronic disease), or to unwillingness or feelings of shame (income, education, alcohol use). However, the main variable in this study, medication use, was recorded directly from the containers, and did not rely on self-report.

Conclusion

It was concluded that benzodiazepine use in this middle-aged population sample remained stable from 1992 to 2002, with a majority of long-term use, despite recommendations in the guidelines for short-term use. Benzodiazepine use remained higher in women, and in respondents with low education, low income, chronic physical disease, functional limitations, depression, anxiety complaints, sleep problems and in those using an antidepressant. More attention should be paid to reduce benzodiazepine use in the middle-aged, in order to diminish its increasing negative effects on health and functioning when getting older. In the case of long-term use, discontinuation programs with a tapering-off procedure may be helpful.

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CHAPTER 8

Summary and General Discussion

In the western world, the proportion of older people in the population is growing. This leads to an increase of late life depression as an important mental health problem. The present thesis aims to investigate particular aspects of depression in later life: the role of gender, social support and medical treatment. It is based on data of the Longitudinal Aging Study Amsterdam (LASA), a community-based study in the Netherlands.

In this chapter, the main findings of this thesis will be presented according to the research questions in the introduction section (chapter 1). In addition, methodological issues of the study are addressed, including the most important limitations and strengths of this study. Implications of the findings for public health and clinical practice are described, followed by some recommendations for future research.

MAIN FINDINGS

The main purpose of this study was to investigate sex differences in depression across older age. In the first part of the thesis, sex differences in the prevalence of late life depression and in symptom profiles were investigated, with particular attention being paid to the influence of socio-cultural characteristics and to risk factors for late life depression. The second part of the thesis aims to investigate drug treatment in late life depression with special attention to gender differences. Antidepressant use and benzodiazepine use in the baseline sample, and changes and trends in the use of these medications in the longitudinal data were investigated, taking gender, demographic aspects and risk factors for late life depression into account.

I a Are there sex differences in prevalence, symptom profiles and risk factors in late life depression? (chapter 2)

In the literature, depression is found about twice as often in women as in men. This is a robust finding for younger adults, but data for older adults are less consistent. A decrease of the gender gap has been proposed (Jorm 1987), but studies often included low numbers of older males, limiting the strength of the results.

In the baseline sample of LASA, with respondents aged 55-85 years old, prevalence of depression in women was almost twice as high as in men. This sex difference was also found in the separate age groups, except in the youngest, aged 55-59 years old. There was no narrowing of the gender gap in the oldest age groups, and the gender differences correspond to those that are found in depression in younger adults. Controlling for age and

for risk factors for depression in older age such as living without a partner, low education, low income, chronic physical disease and functional limitations, reduced the female preponderance by about half but the gender difference remained statistically significant.

In the literature, depressed women are often found to report other and more symptoms than depressed men. Men report more somatic complaints, whereas women would report more affective symptoms, and they are supposed to talk more easily about their feelings and emotions. We could not confirm these supposed gender differences in symptom profiles in our data. Analysis of the items of the CES-D scale showed a rather similar pattern of responding in depressed men and women, in the subscales as well as in the separate items, with the only exception for the question on 'crying', with women crying more often than men.

Concerning the risk factors for depression in late life, gender differences were found in the vulnerability and in the exposure to these risk factors. Remarkably, men who were not or no longer married, with a low income, and receiving low emotional support, were found to have a higher risk for depression than women with these risk factors. However, the exposure to these and other risk factors, such as low education and the presence of chronic physical diseases and functional limitations, was much higher in women than in men, which explained the higher rates of depression in women in LASA despite a lower vulnerability for depression in women.

I b Is religious denomination a symptom-formation factor in late life depression and do gender differences play a role? (chapter 3)

When considering cultural factors influencing mental health problems, religious tradition has been shown to be a vulnerability factor as well as a protective factor in depression. Religious denomination influences social and moral life, and represents an important cultural resource for older adults. Due to expected differences between Calvinists (Protestants), Roman Catholics and non-religious persons in expressing emotions and in dealing with guilt and feelings of individual responsibility, it may also influence symptom profiles in late life depression.

In our study sample, Calvinists suffered less depression than Roman Catholics and non-church members. In the depressed subsample, Calvinists had higher scores on inhibition (could not get going, everything is an effort, talked less) and vegetative symptoms (e.g. loss

of appetite, sleep problems, trouble concentrating, being bothered) than Roman Catholics and non-church members. Even depressed non-church members with at least one Calvinist parent had higher scores on inhibition and vegetative symptoms than those without religious roots. The denomination differences were related to gender, and were found only in men. High levels of feelings of guilt were found in Calvinists as well as in Roman Catholics and may be a common characteristic of traditional Christian religion, with responsibility, duty and guilt awareness being important values.

I c Are there gender differences in the relation between late life depression and social support? (chapter 4)

Lack of social support is a risk factor for late life depression. Living without a partner, having a small network size, and low emotional and instrumental support are associated with depression. Not only the amount but also the meaning and impact of social support are important in the relation with distress, and men and women are found to be different in this respect. Women of all ages have a larger personal network and receive more social support, which is a protective factor against depression. However, a large network also provides a greater opportunity for negative interpersonal experiences, such as the death of someone close. In addition, women are more sensitive to life events occurring to other persons. Men and women differ in amount and need for social support, which may be related to gender differences in depression.

In our study, older men without a partner in the household were more often depressed than older women, and they had a higher risk of developing a depression in the course of the study. Low emotional support received was associated with the presence of depression in men but not in women. A small network predicted onset of depression in men but not in women.

A high need for affiliation was associated with the presence of depression in women, but it did not predict onset of depression in either gender. In a subgroup with low social support and high affiliation need, high rates of depression were found, particularly in men.

II a The use of antidepressants and benzodiazepines in late life depression (chapter 5)

Although response to treatment is favourable in late life depression, undertreatment in higher age is a major problem. Difficulty in diagnosing depression in older persons and the comorbid presence of cognitive impairment or physical disease may have a role in not

providing adequate treatment. Also, the assumption that depression in older people is a normal reaction to stress or to ageing itself may hamper proper treatment.

In our study, investigation of the depressed subsample at baseline showed a low use of antidepressants, not only in respondents with relatively mild depressive syndromes (2%), but also in the subgroup with major depressive disorder. In this group specific treatment is indicated, but only 16% of the participants used an antidepressant, and we had no indications that the other 84% were treated with psychotherapy. At the same time, antidepressant use was even lower when respondents were older, or when they had cognitive impairments. A sex difference was found, with antidepressant use in men twice as high as in women (25% vs.14%). Furthermore, only a quarter was using a daily dose that was considered high enough to be of therapeutic significance. A concerning finding was that benzodiazepine use in this depressed subsample was higher than antidepressant use with 8% in mild depression and 24% in major depressive disorder, with a slightly higher use in women. Benzodiazepines are not considered adequate treatment in depression, may even worsen depressive symptoms such as low mood, concentration problems and lack of energy and may have serious consequences like falls. It was concluded that the majority of older people lacked adequate pharmacological treatment of their depression.

II b Time-trends in antidepressant use (chapter 6)

In the past two decades, antidepressant use in adults in the Netherlands has increased, mainly due to a rise in SSRI use after their introduction in the Netherlands, in the beginning of the nineteen nineties. Considering the undertreatment in older people with depression both in the literature and in our study at baseline 20 years ago, the increase of studies on prevalence and consequences of depression in older people, and the development of more elaborate treatment guidelines especially adjusted for late life depression, the question was if this increase in antidepressant use was also found in older people.

In our study, time trends in the use of all types of antidepressants (SSRI's, tricyclic antidepressants, atypical antidepressants and lithium) were investigated for the period 1992-2002, in respondents aged 65-85 years at each measurement. We paid particular attention to the use of SSRI's, daily doses of the medication, and differences in subgroups. An increase of antidepressant use in general was found in all respondents, with a two-fold increase in the group with major depression (from 15% in 1992 to 30% in 2002) and in the not-depressed group (from 2% to 4%), and the largest increase in the group with minor depression (from

3% to 12%). This increase in use of antidepressants was mainly due to a sharp rise in SSRI use. Prescribed daily dosages became more adequate in this period, except for the tricyclic antidepressants, dosages of which were still low (10-20 mg daily) in over half of the users. A relatively larger increase in antidepressant use was found in the oldest respondents. In the group with major depression, antidepressant use was lower in the presence of comorbid cognitive impairment, functional limitations, or chronic physical illness.

II c Time-trends in benzodiazepine use (chapter 7)

In addition to the growing knowledge on the treatment of depression and anxiety in the past decades, the awareness of the negative consequences of long-term benzodiazepine use has increased. Benzodiazepine use may lead to addiction problems and side effects such as mobility problems, falling, sedation and cognitive problems, particularly in older age. The question addressed in this thesis is if these new insights have led to a decrease in benzodiazepine use, in particular a decrease in prolonged use, and in vulnerable groups such as older persons.

In our study trends in benzodiazepine use (anxiolytic drugs and sleeping pills) between 1992 and 2002 were investigated in two population-based samples aged 55-64 years. Although a decrease in benzodiazepine use was expected, it was found to be stable over these 10 years, with 8% in both samples, with the same numbers in the subgroups with anxiety or sleep problems. The majority used the medication longer than 1 year, with even a slight increase instead of the expected decrease (70% in 1992 and 80% in 2002). More favourable was the increase of short-acting benzodiazepines without pharmacologically active metabolites in this period, from 55% to 65% among users. No change was found in factors that were associated with higher benzodiazepine use at baseline, such as being female, having lower education or lower income, and the presence of chronic physical diseases, functional limitations and cognitive impairment. Also, the presence of depression remained associated with (long term) benzodiazepine use, which may lead to worsening of depressive symptoms.

IN SUMMARY

This thesis demonstrates the diversity of depression in late life and the challenges for improving treatment.

Gender and age have their own unique association with depression, but they also interact

with socio-cultural factors that influence prevalence and onset of depression, such as education, income, marital status, religious denomination, network size and different types of social support. Most of these factors are unequally distributed across gender. Furthermore, considering the differences in vulnerability for and exposure to individual risk factors for late life depression, it is clear that all these aspects must be taken into account when diagnosing and treating depression in late life.

Pharmacological treatment in late life depression showed some improvement for the period under study, with the introduction of SSRI's giving the oldest old the benefit of increasing antidepressant use in the case of depression. However, in the more severe depressive syndromes, only a minority used antidepressants. Benzodiazepine use did not decrease despite the growing knowledge of the negative consequences of long term use, particularly in older people.

METHODOLOGICAL CONSIDERATIONS

This thesis was based on data from the Longitudinal Aging Study Amsterdam (LASA). The LASA study was initiated by the former Dutch Ministry of Welfare, Health and Culture, in the early 1990's, with the purpose of gaining information about the expected demographic and health-related changes and needs in the older population due to increasing life expectancy. The study was set up as a longitudinal, interdisciplinary study with as its main purpose the investigation of the predictors and consequences of changes in autonomy and well-being in the Dutch aging population and started in 1992. Ten years later, a second cohort, called LASA II, was added, using the same sampling procedures as the original LASA study (now called LASA I), with the purpose of the investigation of cohort effects and differences between LASA I and LASA II. In this thesis, baseline data, follow-up data and data from the second cohort of the LASA study were used.

There are several methodological issues that should be considered. In this paragraph, the most important strengths and limitations of the present thesis will be described, paying specific attention to sampling procedures, management of non-response and attrition, information bias, measurement of depression and medication, and the comprehensiveness of the data set.

Sampling and non-response

The LASA cohort is based on a nationally representative sample of older adults aged 55-85

years, with birth years 1908-1937, from both urbanized and rural areas in three geographic regions in the Netherlands that provide an optimal representation of the main religious denominations (Protestant, Catholic and secular). The sample was first used, early 1992, in another study on living arrangements and social network, called NESTOR LSN, and then in LASA. The sample was recruited from 11 municipal registries. It was stratified for age, sex, and expected mortality 5 years into the study, with an oversampling of older people, and older men in particular. The initial response rate in NESTOR LSN was 60% (*n*=3805). The response rate in the first LASA-cycle was 85% of the respondents of NESTOR LSN with a cooperation rate of 89%, resulting in 3107 respondents. A second cohort was recruited in 2002/2003, exactly 10 years after the first LASA cycle, using the same sampling frame. Response rate was 55%, resulting in a cohort of 1002 respondents aged 55-65 years, with birth years 1938-1947. Detailed information on sampling procedures and response rates in NESTOR LSN and LASA has been described by Huisman et al (Huisman, Poppelaars et al. 2011).

The interviews were in Dutch, and respondents who did not speak Dutch well enough to participate were not included. Therefore, generalization of the results to older people of some ethnic minorities is limited. Non-response at the initial invitation to participate in the LASA-study was mainly due to refusal (10.4% of the sample), and further to health problems (ineligible: 3.5%), being deceased before being approached (3.3%) and not contacted (1.2%). Refusal and ineligibility were related to age, with older sample members refusing more often to participate in (parts of) the study or scoring 'ineligible' as a reason for non-participation (both $p<0.001$). Male sample members from the oldest cohorts were more often deceased at contact time ($p<0.001$). The problem that non-response may be unequally distributed across age and sex, was addressed by means of the sampling procedures in LASA, with stratification for age and sex, and oversampling of older males. Many studies in older people are lacking sufficient numbers of older males. A particular strength of the LASA data is the high number of older males in the sample at baseline, and, due to the oversampling, also in the follow-up data, which makes the LASA-data particularly suitable for investigation of different age groups and both sexes within the older population.

Loss to follow up

Attrition at follow-up in LASA was about 15-20% per cycle, and was mainly due to mortality, with rates of 12-15% between the consecutive cycles, and to lesser extent to other causes such as refusal, frailty or no contact (together about 5%). Apart from the respondents who

died or could not be contacted, most respondents were remarkably steadfast throughout the years, and many participated for 10 years or more in the LASA study, thus providing us with a unique data collection for longitudinal research purposes. Although high mortality is a normal characteristic of an older population, in LASA it was related to several outcome measures and predictors, and therefore it may bias the results of our study. Attrition (due to mortality as well as other causes) was higher in men and in older age, and was associated with low education (primary education or less), the presence of two or more chronic physical diseases, and cognitive impairment (MMSE <24). Detailed information on attrition has been described in the separate chapters in this thesis, and by Deeg (Deeg, van Tilburg et al. 2002) and Huisman (Huisman, Poppelaars et al. 2011) .

By stratification for age and sex, and the oversampling of old men at the start, sex and age groups remained large enough for our investigations. However, relative underrepresentation of respondents with low education, two or more chronic physical diseases and cognitive impairment may have influenced the results in the prospective study on social support and depression (chapter 4), and in our studies on the time trends in antidepressant use and benzodiazepine use (chapters 6 and 7). All three conditions were associated with depression, with less use of antidepressant medication, and with female gender, and their underrepresentation may therefore have weakened the association of gender and depression (chapter 4) and the association of gender and antidepressant use (chapter 6). Low education appeared to be connected with higher benzodiazepine use. Its underrepresentation may lead to a lower rate of benzodiazepine use in the follow up samples, thus weakening the finding of stability of benzodiazepine use over time (chapter 7).

Information bias

Information bias results from incorrect gathering of information or determination of outcome (Grimes and Schulz 2002). In LASA, interviews and self-report scales were used, and systematic errors in these measurements may lead to misclassification of variables and to under- or overestimating the strength of the results. When this type of information bias differs between groups, it may compromise the internal validity of the study. In the literature, report bias and recall bias in the measurement of depression is often found, with differences between men and women in reporting symptoms in the present and recalling depressive episodes in the past. Women are found to report more symptoms than men with the same severity of the depression, and women are found to have a better memory for depressive episodes in the past (Angst and Dobler-Mikola 1984). Due to these two forms of

information bias, depression in the present and the past may be overestimated in women and underestimated in men.

Depression itself may also lead to report bias in the measurement of other variables, due to a tendency of the depressed respondent to report more negatively about the past, or about current health status and functioning.

In LASA, these types of information bias may play a role. However, the design of the study, with a structured interview, training of the interviewers, monitoring of the interviews by checking the audiotapes, and the use of semi-structured diagnostic interviews for psychiatric diagnoses, makes information bias less likely to occur because these methods reduce the risk of large differences in the way interviewers gather information. Nevertheless, information bias due to variation in the way respondents give information and answer questions will remain. Sex differences in (reporting) depressive symptoms are among the main topics of this study, and are discussed in the preceding chapters. Further detailed information on possible information bias is reported in the individual chapters of this thesis, focused on specific research questions.

Measurement of depression

Attention should be paid to the definition and measurement of depression. At the time that the design for LASA was set up, late life depression was poorly defined and researched, and the DSM-criteria for major depression did not seem to fit very well in older persons (Snowdon 1990). Therefore, a two-stage design was used, starting with screening on a broadly defined 'clinically relevant depressive syndrome' and followed by case diagnosis according to DSM-criteria. This depressive syndrome was measured with the Center for Epidemiologic Studies Depression Scale (CES-D), a self-report questionnaire developed for screening on depressive symptomatology in the community and suitable for older adults because of minimal overlap with physical disease (Berkman, Berkman et al. 1986),(Radloff 1977; Radloff and Teri 1986). The CES-D consists of 20 items, with scores ranging from 0-60 and a cut-off point of 16. In LASA, the CES-D was not used as a self-administered questionnaire, but was part of the main face-to-face interview. Sensitivity for major depression was found to be 100% and specificity 88% (Beekman, van Limbeek et al. 1994; Beekman, Deeg et al. 1997). The CES-D showed satisfactory psychometric properties in LASA with Cronbach's alpha = 0.87 .

In the respondents scoring 16 or higher on the CES-D, a diagnostic interview was performed using the Diagnostic Interview Schedule (DIS) (Robins, Helzer et al. 1981), to investigate the presence of a mood disorder according to the DSM-criteria: major depressive disorder or dysthymic disorder. Respondents without a depressive disorder according to the DIS, but with a score of 16 or higher on the CES-D, were considered to have a so-called subthreshold depression (Blazer, Kessler et al. 1994) (Tannock and Katona 1995). This subthreshold or minor depression has been found to be a clinically relevant depressive syndrome in older people, resulting in disability, decreased well-being and increase of service utilization (Beekman, Deeg et al. 1997). Therefore, this group was included in the study next to the Major Depressive Disorder group.

Measurement of medication use

Pharmacological treatment was assessed by recording the medication of the participants directly from the containers in the home of the respondents. By this method, false inclusion of medication prescribed but not taken was precluded, and we also registered medication without prescription, the so-called over-the-counter (OTC) medication which may include important drugs such as pain medication and corticosteroids. The interview structure allowed the listing of 8 different drugs, and the psychopharmacological agents were assessed first, to ensure complete information on these medications. The anatomical-therapeutical-chemical (ATC) coding and categorization system for medication was used to classify all medication (Pahor, Chrischilles et al. 1994). All antidepressants, including lithium, and all benzodiazepines (anxiolytics and narcoleptics) were classified, and checked for correct doses and prescription schemes. Duration of use was also investigated.

A limitation of this survey was that we had no information about the indication for the medication, which is particularly important for the antidepressants. SSRI's are also used in anxiety disorders. However, anxiety and depression are often found together, so the prescription of an SSRI may be for both conditions. TCA's are also used for sleep problems or as pain medication, but in lower doses than when prescribed in depression. Another limitation was that information on serum levels of the antidepressants was not available. When TCA's are prescribed, serum levels are necessary to determine if the dosage is therapeutic. For SSRI's there is no particular therapeutic range, but serum levels may be helpful to distinguish people who are slow or rapid metabolizers and therefore in need of adjusted dosages. In the separate chapters 5 and 6 we described in detail how these limitations were dealt with.

Comprehensiveness of the data set

The LASA study was designed by researchers from social and biomedical sciences, and their close collaboration ensured a thoroughly multi-disciplinary approach. Due to the sampling and measurement procedures, the LASA data are of a high quality. They cover a broad range of domains that are known to be interrelated and influence each other (physical, cognitive, emotional and social functioning). The follow-up data of almost 20 years allow investigation of changes and trajectories, whereas the addition of the second cohort 10 years later allows investigation of cohort effects and differentiation between cohort effects and age effects. These strengths made the LASA data particularly suitable for investigation of depression. The different aspects of the LASA data served the purpose of providing information for government policy on health care and services for older people, and made LASA a reliable resource for fundamental research on aging.

For the present thesis, the LASA data allowed a detailed investigation of associations between depression and several demographic characteristics and aspects of the other domains, in both sexes and in several age groups, and in a cross-sectional as well as a longitudinal design.

There are limitations as well. Depression is known to show variation within weeks or months, so for some purposes, the interval of 3 years is too long. Another problem is the inability to study specific characteristics or trajectories in detail due to small subgroups when it comes to specific disorders, such as antidepressant use in the subgroup of severely depressed men (chapters 5 and 6) or the development of depression in men with a small network (chapter 4).

RELEVANCE AND IMPLICATIONS FOR CLINICAL PRACTICE AND THEORY

The present thesis shows the pervasiveness of sex differences in depression in later life, with women being twice as often depressed as men in older (and very old) age, and with rates similar to those in younger adults. Neurobiological aspects including hormonal changes, psychological factors and coping style, socio-cultural factors, and the interplay between these aspects, all have a role in the emergence and persistence of the gender gap, and make it an authentic and important aspect of late life depression.

We demonstrated that symptom profiles of older depressed men and women are very much alike, with similar patterns in affective and somatic symptoms. Thus, in clinical practice,

the usual procedures of diagnosing depression in late life can be used, with gathering information about all kind of symptoms of depressed mood and somatic complaints in both sexes, and with the knowledge that the preponderance of women will be present in all adult ages.

In this thesis, the importance of gender in religious denomination was shown with depressed Calvinistic men reporting more somatic than affective complaints, which may increase the risk of missing the diagnosis of a depressive syndrome. Therefore, it is important to establish any religious denomination and to pay special attention to Calvinistic men. The report of high feelings of guilt by persons of any denomination calls for further exploration to decide if this is a symptom of depression.

We showed that risk factors for late life depression are complex and diverse in their effects when it comes to gender differences. Loss of the partner, low income, physical diseases and functional impairment increase the vulnerability for depression in men, but the exposure to these risk factors is higher in women. So, it is important to identify these risk factors, and then to be aware of the different impact that they have in men and in women. Similar considerations apply to social contacts, which are found to have a protective effect for men, but may be protective as well as disruptive for women, depending on other factors such as problems of other persons in the network and feelings of responsibility towards these persons. When women report that emotional support is very important, this may be a symptom of an underlying depression and warrants further exploration of mood problems.

The present thesis also shows that although a small improvement was found over the past two decades, the majority of older depressed people still does not receive adequate pharmacological treatment, even in a major depressive episode which is considered to be an indication for pharmacologic intervention. Particularly low rates of antidepressant use and inappropriate benzodiazepine use were found in depressed older women. Maybe this inadequate treatment is due to not recognizing the depressive disorder, or to hesitation to provide proper treatment; there is no doubt that it is a serious problem. It may cause unnecessary suffering of the depressed person and his or her environment, and it may severely hamper mental and physical well-being.

The findings of this thesis may be relevant in several domains of mental health in later life and late life depression in particular.

The first important domain is *defining and diagnosing depression*. An important topic of discussion in research and in clinical practice is the broad and indistinct definition of depression within the current classification system of the DSM, with different levels of severity, lacking information on aetiology and course patterns, and often providing an inadequate fit for older people, cultural minorities, children, etc.. At the same time, the DSM-criteria appear to be too narrow, for example when considering anxiety symptoms, which are often seen in depression, but which in the current system have to be diagnosed separately (Paykel 1972; van Balkom, Beekman et al. 2000). It seems to be more appropriate to discern subgroups of affective disorders and to think along lines of dimensions of duration and severity instead of counting numbers of (a fixed and rather limited amount of) criteria. Other parameters such as personality characteristics (high neuroticism), level of functioning, age and somatic illnesses may be helpful to improve the distinction between several types of depression (Shankman and Klein 2002). In our study, the combination of gender with several characteristics (being widowed, low income, somatic illness, functional impairment, low emotional support and Christian denomination) was found to be helpful in discerning groups with higher rates of clinically relevant depressive syndromes, even when they did not fulfil DSM criteria.

When it comes to *applying adequate treatment*, the notions mentioned previously are of course of vital importance: a diagnosis is needed to start treatment. However, research on depression and experiences in clinical practice make it clear that not every one with a diagnosis of depression benefits from (the same form of) treatment, and that severity of the depression is an important parameter (Fournier, DeRubeis et al. 2010). In milder forms of depression, a more basic and general approach is advised. This can be performed very well by a general practitioner or a general mental health professional such as a trained nurse, and consists of life style advices and short, pragmatic counselling (Baldwin, Anderson et al. 2003). In more severe depressive disorder, more specific treatment options are indicated and effective, such as antidepressants, cognitive behaviour therapy or interpersonal psychotherapy and electro-convulsive therapy (Pinquart, Duberstein et al. 2006).

Another important domain is *prevention*. Psychological and psychiatric problems are responsible for a large part of the disease burden in the Netherlands and other Western countries, and bring about vast economical costs and widespread use of health care services. Adequate treatment will never ban depression fully, and prevention in psychiatry, and more specifically, prevention of onset, worsening and relapse of depressive episodes, has gained

more attention in the last decades. Selective prevention and indicated prevention seem to be the most effective forms of preventing new episodes of depression (Cuijpers, Van Straten et al. 2005). According to the results in our study, several characteristics are appropriate for use in programs of selective prevention of depression in older persons, with the notion that the separate risk factors are important, but their combinations probably even more so. Suitable indicators for selective prevention are the following parameters: female sex, also in older age; loss of the partner and low income with particular attention being paid to older men; and low social and emotional support in older men and women, with special attention to stress related to the social network in women.

DIRECTIONS FOR FUTURE RESEARCH

The growing body of population-based and clinical studies on late life depression in the last decades, including the studies presented in this thesis, has led to an increased understanding of the diversity of mood problems in clinical presentation, severity and course in older people, and insight in the variety of predictors and consequences for autonomy and well-being. The knowledge that depression is a common mental health problem, and that it is responsible for a considerable part of the burden of disease worldwide, also in older adults, merits further research on distinguishing subgroups in the older population with elevated risk for depression and for an unfavourable course.

Future research should further improve this understanding and should give directions how to optimize diagnostic procedures and treatment processes. As mentioned above, of particular interest is the development and application of preventive measures for persons who are at risk for developing depression, for persons with prodromal or mild depressive symptoms, as well as for persons somewhere in the depression-trajectory after having experienced one or more depressive episodes.

In the present study, subgroups with depression were too small to enable further investigation of particular risk factors in these groups. Enlargement of statistical power can be obtained by combining population studies, which has already been done in the EURO-DEP project (Beekman, Copeland et al. 1999; Blazer 1999; Copeland 1999). In EURO-DEP, 14 European countries collaborate on late-life depression in population-based studies. Although in the participating countries different age groups and different measurement methods were used, it has been possible to merge the separate data sets to one large data set suitable for the investigation of depression and risk factors., e.g. the study in EURO-DEP on depression and

parkinsonism (Braam, Beekman et al. 2010). CLESA, another cross-national collaboration on mental health with five European countries and Israel, investigated country-specific gender differences in depression (Zunzunegui, Minicuci et al. 2007). Another example is the ESEMeD project (European Study of the Epidemiology of Mental Disorders), in which mental health in adults in six European countries was investigated (Alonso, Angermeyer et al. 2004). Further exploration of late life depression in subgroups based on gender, age, demographic factors en socio-cultural characteristics should be performed in these composite data sets.

The results from several, combined studies on depression in the older population may be helpful in the search for a more tailored approach in selective prevention.

Further exploration in the subgroups mentioned above is important for the development of indicated prevention: the identification of older persons with a prodromal or a subthreshold depression in the population, with the purpose of preventing or minimizing the development of a full-blown depression and to reduce the negative consequences and the diminished quality of life that are seen in the subthreshold depression state. Tests and screeners must be developed, to detect persons in prodromal and subthreshold state. Identification of persons at risk and persons with prodromal or subthreshold depression is not enough, however. We also need to distinguish several grades from high to low risk of developing or converting into a particular subtype of depressive disorder. Therefore, an algorithm should be developed which consists of weighted socio-demographic characteristics, risk factors and protective factors, and several aspects of late life depression, like symptom-profile, severity, course and duration.

In our study only small groups with more severe depressive syndrome were present. To develop a more tailored approach in diagnostic procedures and treatment options for the people who already developed a depressive disorder, it is necessary to learn more about this severely depressed group, and this warrants collaboration with research in clinical populations, such as NESDO (Netherlands Study on Depression in Older age) (Comijs, van Marwijk et al. 2011). NESDO is a Dutch multi-site naturalistic prospective cohort study which allows examining the determinants, the course and the consequences of depressive disorders in older persons over a period of six years, and to compare these with those of depression earlier in adulthood. Within NESDO, information is gathered on remittance, relapse and duration of depressive episodes, and on predictors of variable outcomes. By

combining clinical data from NESDO (age of onset, genetic vulnerability (familial load), severity, type of symptoms, duration and course), with the epidemiological data from LASA and EURODEP, subtypes of depression can be defined with a particular profile, and, we do hope, a more specified treatment programme with relapse prevention.

There are some particular challenges for depression in older adults. The first big issue is the diversity in later life when it comes to general aspects such as physical health, education and working career, social functioning, capacity to cope with problems and threats, and resilience.

In this diversity, biological age plays an important role, and seems to be of greater importance than calendar age. A person of 62 years old with diabetes, an unhealthy life style and a small social network may have the vulnerability to chronic physical problems and functional impairment, similar to people aged 75 or older. On the other hand, we all know the very healthy person above the age of 80 who is in very good physical and mental shape, and socially active. This means that, if we want to use the factor 'age' in algorithms that predict development, type and course of depressive disorder, we should use a kind of indicator for biological age in addition to calendar age which is normally used. Another problem is that in the presence of a risk factor for depression, resolving or mitigating this factor is less easy than it seems. For example, a small social network, which is a risk factor for depression in older age, does not always mean that the person is or feels lonely, and in addition, loneliness is not so easily solved by organising activities or more social contacts. A study on interventions in older adults who reported to be lonely showed that only a few interventions changed their feelings of loneliness (Fokkema and van Tilburg 2007). For many older people, loneliness seem to be kind of state that one may be in for shorter or longer period of time, and when it is not possible to change this state, people tend to accept it and wait for better times (Schoenmakers, van Tilburg et al. 2012). For some people this may be the best way of coping, but for others a more active approach could be preferable. The question is then: how can we determine what intervention should be given to whom?

Thus, just like depression itself, factors that seem to be important in late life depression are not so easily dealt with and are in need for further differentiation themselves before they can be used in prevention and treatment programmes. Further differentiation, not only of depressive symptomatology and course, but also of the associated factors, is needed.

Then, last but not least some considerations on gender and depression. The findings in this thesis underscore those in the literature on gender and depression in younger adults. In the field of neurobiology, the concepts of the gender specific gene-environment interaction and the sexual dimorphic stress response have to be elaborated further. Because estrogens seem to play a role in the stress response, it is of particular interest to also include older persons in these investigations: changes in estrogen levels and the diminished cyclic variability after menopause may help to investigate the neuro-endocrine stress system and the role of estrogens. The differences in coping style between women and men should become part of the prevention programmes, because they seem to be associated with the differential risk for depression. The same is true for social relations, with the ambiguous impact of a large network on women, and the higher impact of loss of the partner and a small network on men.

CONCLUSION

Up to high ages, women are twice as often depressed as men. Depression can be diagnosed in the same way in men and women, because their symptom presentation is rather similar. The gender differences in coping style and in the vulnerability and exposure to several risk factors warrant a differential approach in the clinical evaluation and treatment and can be applied in elaborated prevention.

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Nederlandse Samenvatting

DEPRESSIE BIJ OUDEREN:
SEKSEVERSCHILLEN IN KLINISCHE PRESENTATIE
EN MEDICATIEGEBRUIK

INLEIDING

Depressie

Depressie komt veel voor, over de hele wereld, en op alle leeftijden. Depressie kan gepaard gaan met allerlei klachten en met aanzienlijk lijden, en kan leiden tot verminderd functioneren op diverse levensgebieden. In ernstige gevallen kan opname noodzakelijk zijn en kan depressie levensbedreigend zijn. Maar ook de lichtere vormen van depressie geven meer problemen dan vaak wordt gedacht. Op dit moment komt depressie wereldwijd op de tweede plaats wat betreft ziektelast, na hart- en vaatziekten, en de verwachting is dat in 2030 depressie zelfs bovenaan zal staan (WHO). Depressie heeft daarmee een enorme impact, niet alleen op het leven van mensen, maar ook op de samenleving als geheel.

Depressie als verstoring van de gemoedstoestand, gepaard gaand met diverse lichamelijke klachten, is al heel lang bekend. In de psychiatrie wordt de 'depressieve stoornis' gedefinieerd volgens de criteria van de DSM, een internationaal classificatiesysteem voor psychiatrische ziektebeelden. Deze definitie is aan verandering onderhevig, maar de verschijnselen 'sombere stemming' en 'afname van interesse, zin en plezier' worden nog altijd beschouwd als de kernsymptomen van de depressieve stoornis. Depressie kan zich op veel verschillende manieren uiten, door een divers scala aan klachten naast één of beide kernsymptomen. Nagenoeg altijd zijn er ook lichamelijke verschijnselen zoals verminderde eetlust, gestoorde slaap en energieverlies, naast nog andere psychische verschijnselen zoals besluiteloosheid en concentratieproblemen, en dat in wisselende combinaties.

Depressie is multifactorieel bepaald, wat wil zeggen dat er niet één oorzaak of aanleiding is, maar meer factoren bijdragen aan het ontwikkelen van een depressief beeld. Aanleg voor depressiviteit is waarschijnlijk al bij de geboorte aanwezig, en kan dan op verschillende momenten en manieren tot uiting komen. Een aanwijzing voor deze genetisch bepaalde kwetsbaarheid is het vaker voorkomen van depressie in bepaalde families. Ook is bij mensen die eerder in het leven een depressieve periode doormaakten, is de kans op het ontwikkelen van een depressie verhoogd. Omgevingsfactoren spelen een grote rol in het daadwerkelijk krijgen van depressieve klachten, de leeftijd waarop dit gebeurt, de soort symptomen en de ernst daarvan. Zo lijkt er een samenhang te bestaan met de aanwezigheid van sommige persoonlijkheidskenmerken (bijvoorbeeld neiging tot afhankelijkheid, tobberige instelling), het ontbreken van een sociaal netwerk, en het meemaken van ingrijpende gebeurtenissen, zoals verlies van een belangrijk persoon of traumatische ervaringen. Ook bij bepaalde

lichamelijke ziekten (zoals de ziekte van Parkinson, schildklierlijden en dementie) komt vaker dan gemiddeld depressiviteit voor.

Sekseverschillen bij depressie

Een opvallend kenmerk van depressie is het verschil tussen mannen en vrouwen. Bij vrouwen komt een depressie twee keer zo vaak voor als bij mannen. Dit verschil is wereldwijd terug te vinden, hoewel het wat kleiner lijkt te zijn wanneer financiële mogelijkheden, kans op werk en sociale rollen gelijkwaardiger zijn verdeeld tussen mannen en vrouwen. Ook de symptomen verschillen: bij vrouwen wordt vaker een toename van eetlust en gewicht en van slaapbehoefte gevonden. Ook hebben depressieve vrouwen vaker slaapstoornissen, energieverlies, angstklachten en lichamelijke klachten. Daarnaast hebben vrouwen vaak een groter aantal depressieve symptomen dan mannen, met daarin verhoudingsgewijs veel lichamelijke symptomen (vitale depressie genoemd). Winterdepressie komt drie keer zo vaak voor bij vrouwen als bij mannen.

Er is veel onderzoek gedaan naar de achtergrond van dit man-vrouw verschil. Diverse factoren lijken een rol te spelen.

Op biologisch gebied blijken diverse hormonen (vrouwelijke geslachtshormonen zoals oestrogeen en progesteron maar ook andere hormonen) invloed te hebben op de stemming. Veranderingen in de geslachtshormonen die optreden bij zwangerschap en bevalling of gedurende de menstruele cyclus hebben duidelijk een relatie met het optreden van depressieve klachten of een depressieve periode. Daarnaast zijn in de aanmaak, werking, en afbraak van andere hormonen die van invloed zijn op de stemming verschillen gevonden tussen mannen en vrouwen.

Op psychologisch gebied lijken verschillen in het omgaan met problemen en opgaven bij te dragen aan het verhoogde risico op depressie. Vrouwen zouden meer geneigd zijn tot piekeren en problemen meer op zichzelf betrekken dan mannen, hetgeen zou kunnen leiden tot depressieve klachten. Ook lijken vrouwen problemen minder actief aan te pakken, hetgeen kan leiden tot een verminderd gevoel van controle over een situatie. Ook dit hangt samen met het krijgen van depressieve klachten.

Op sociaal gebied dragen de vaak minder gunstige sociaal-economische positie, sociale status en rol van vrouwen ten opzichte van mannen bij aan het verschil in depressie, evenals geweld (en specifiek seksueel geweld) tegen vrouwen. Daarnaast spelen sociale steun en

sociale netwerken een rol. Vrouwen hebben vaak meer sociale steun en grotere netwerken dan mannen, hetgeen beschermt tegen depressie, maar tegelijkertijd geeft dit ook meer zorgen en verantwoordelijkheden, zodat er ook een negatief effect van sociale contacten kan ontstaan.

Tenslotte is geopperd dat het man-vrouw-verschil mogelijk niet echt bestaat, maar een meetfout is, bijvoorbeeld doordat vrouwen vaker over hun emoties praten, depressieve klachten gemakkelijker erkennen, en eerder hulp zoeken dan mannen. Dit verklaart inderdaad een deel van het man-vrouw-verschil, maar zeker niet geheel.

Depressie bij ouderen

Ook bij ouderen komt depressie veelvuldig voor: ongeveer 14% van de mensen boven de 55 jaar maakt één of meer depressieve periodes door. Een depressie op oudere leeftijd voldoet maar bij 2% aan de criteria van een depressieve stoornis volgens de bovengenoemde DSM. Echter ook de 'lichtere' vormen bij de overige 12% kunnen wel degelijk leiden tot een slechtere kwaliteit van leven, een toename van beperkingen en handicaps in het dagelijks leven, een toegenomen gebruik van voorzieningen en een forse belasting van de omgeving.

Naast de algemene risicofactoren voor depressie, zoals de boven genoemde persoonlijkheidskenmerken, het ontbreken van sociale steun en ingrijpende gebeurtenissen, zijn er risicofactoren waar vooral ouderen mee te maken krijgen. Dat zijn bijvoorbeeld het verlies van de levenspartner, en het krijgen van lichamelijke ziekten die met beperkingen gepaard gaan. Veel ouderen gebruiken medicijnen, en depressie kan een bijwerking zijn.

Sekseverschillen bij depressie bij ouderen

Over sekseverschillen bij depressie bij ouderen is niet zoveel bekend als bij jongere volwassenen. Onderzoeken naar het man-vrouw verschil in het vóórkomen van depressie bij ouderen laten wisselende resultaten zien, variërend van verdwijnen tot gelijk blijven van het verschil. Ook is onduidelijk of de verschillen in symptomen, zoals gevonden bij jongere volwassenen, ook op oudere leeftijd aanwezig zijn.

Er zijn wel sekseverschillen gevonden in de risicofactoren voor depressie. Zo krijgen oudere vrouwen vaker depressieve klachten dan oudere mannen bij langdurige financiële problemen en als er sprake is van weinig sociale contacten en sociale steun. Net als op jongere leeftijd hebben ook oudere vrouwen meer last van problemen van anderen.

Daardoor kan een groot sociaal netwerk of een fijne partnerrelatie toch veel stress opleveren, en bijdragen aan het ontstaan van depressieve klachten. Aan de andere kant hebben oudere mannen vaker depressieve klachten dan vrouwen bij het verlies van de levenspartner, als zij een laag inkomen hebben en bij weinig emotionele steun. Behalve gevoeligheid voor de risicofactoren speelt het vóórkomen daarvan een rol. Sommige risicofactoren komen veel vaker voor bij vrouwen dan bij mannen (bijvoorbeeld verlies van de levenspartner, lichamelijke beperkingen door ziektes en een laag inkomen).

Behandeling van depressie bij ouderen

Zonder behandeling is het beloop van de depressie bij ouderen ongunstig. De klachten kunnen lang aanwezig blijven en ook weer terugkomen na een eerste verbetering.

Zowel medicamenteuze behandeling als psychotherapie is effectief gebleken bij depressie op oudere leeftijd, vooral bij de ernstiger vormen. Bij zeer ernstige en therapieresistente depressies bij ouderen levert Electro-convulsieve therapie (ECT) goede resultaten op.

Uit de literatuur blijkt echter dat depressie bij ouderen vaak onvoldoende of helemaal niet wordt behandeld, zelfs als er ernstige klachten zijn. Redenen daarvoor kunnen zijn dat de depressie niet wordt herkend, dat de depressieve klachten worden toegeschreven aan een lichamelijke ziekte (bijvoorbeeld de ziekte van Parkinson) of dat er geen antidepressivum wordt gegeven vanwege lichamelijke ziekte of het gebruik van andere medicijnen. Daarnaast wordt nogal eens een te lage dosis van het antidepressivum gegeven, of wordt het niet lang genoeg gebruikt.

Psychotherapie wordt niet vaak aangeboden aan depressieve ouderen terwijl onderzoek laat zien dat bepaalde vormen heel effectief zijn. Het (nog) onvoldoende beschikbaar zijn van psychotherapeuten met ervaring in de behandeling van ouderen speelt daarbij waarschijnlijk een rol.

OPZET VAN HET ONDERZOEK

Vraagstelling

Gezien het veelvuldig voorkomen van depressie bij ouderen en de grote ziektelast die dit met zich meebrengt, is gedetailleerde kennis van dit ziektebeeld van groot belang voor goede diagnostiek en passende behandeling.

Uitbreiding van de kennis van het vóórkomen, de symptomatologie en de risicofactoren van depressie in de verschillende groepen ouderen (zoals mannen en vrouwen) is belangrijk voor het tijdig herkennen van depressieve symptomatologie en ook bij het opzetten van preventieprogramma's.

Inzicht in de huidige stand van zaken in de behandeling van depressie is nodig voor het optimaliseren daarvan. In de afgelopen 20 jaar zijn er nieuwe antidepressiva op de markt gekomen, die mogelijk geschikter zijn voor ouderen, en het is dan ook belangrijk om te onderzoeken of ouderen daarvan profiteren.

Het onderzoek in dit proefschrift richt zich specifiek op deze twee aspecten van depressie bij ouderen, namelijk

- (i) de verschillen en overeenkomsten tussen vrouwen en mannen wat betreft vóórkomen, symptoomprofielen en risicofactoren van depressie, en het verband tussen depressie en sekse aan de ene kant, en geloofsovertuiging en sociale steun aan de andere kant, en de medicamenteuze behandeling

- (ii) het gebruik van antidepressiva en kalmeringsmiddelen en veranderingen in dit gebruik in de afgelopen 20 jaar

De Longitudinal Aging Study Amsterdam

Het onderzoek van dit proefschrift is uitgevoerd binnen de Longitudinal Aging Study Amsterdam (LASA). LASA is een multidisciplinair, longitudinaal onderzoek naar voorspellers en gevolgen van veranderingen in autonomie en welbevinden in de ouder wordende Nederlandse bevolking. LASA richt zich daarbij op lichamelijk, cognitief, emotioneel en sociaal functioneren. LASA is gestart in 1991 op verzoek van het ministerie van (indertijd) VWS om zicht te krijgen op de benodigde gezondheidszorg en andere voorzieningen voor ouderen in de nabije toekomst, vanwege de voorspelde vergrijzing van de Nederlandse samenleving.

Vanuit de bevolkingsregisters van drie regio's in Nederland is in 1992 een gerandomiseerde steekproef getrokken van mensen van 55 tot 85 jaar. Deze was gestratificeerd naar leeftijd en geslacht, met een oververtegenwoordiging van mannen en de oudste ouderen, zodat deze in de loop van de studie in voldoende mate in de steekproef aanwezig zouden zijn. Aan het eerste LASA interview (T1) namen 3.107 mensen deel. Sindsdien zijn er elke drie

jaar vervolgmetingen gedaan: T2 (1995/1996) met 2.545 deelnemers, T3 (1998/1999) met 2.076 deelnemers en T4 (2001/2002) met 1.691 deelnemers. In 2002/2003 is een tweede groep van 1002 deelnemers geworven (LASA II) met leeftijd 55 tot 65 jaar. Hierdoor werd vergelijking tussen groepen mogelijk, en kon de inmiddels uitgedunde eerste LASA-groep worden aangevuld.

Elke meting bestond uit een hoofdinterview, een aanvullende schriftelijke vragenlijst en een medisch interview met bloedonderzoek, bij de deelnemers thuis, door getrainde interviewers. In de meting werd een grote hoeveelheid informatie verzameld, waaronder de in deze studie gebruikte gegevens over depressie, geloofsachtergrond, sociale steun en medicatiegebruik. Depressie werd in twee stappen gemeten: eerst via screening op klinisch relevante depressieve klachten, en vervolgens bij een kleinere groep met een diagnostisch onderzoek volgens de DSM.

RESULTATEN

Deel 1: Sekseverschillen bij depressie bij ouderen

In de eerste drie hoofdstukken na de inleiding staan de verschillen (en overeenkomsten) tussen oudere vrouwen en mannen met depressieve klachten centraal.

In *hoofdstuk 2* werd eerst onderzocht of het sekseverschil in het vóórkomen van depressie, zoals dat bij jongere volwassenen is gevonden, ook op oudere leeftijd blijft bestaan. Dat bleek inderdaad het geval: vrouwen waren bijna twee keer zo vaak depressief als mannen, en dat gold voor alle leeftijdsgroepen behalve voor de jongste groep (55-59 jaar), waarin het ongeveer gelijk was. Na correctie voor demografische en risicofactoren nam het verschil wel iets af, maar bleef statistisch significant.

Vervolgens werd onderzocht of er verschillen waren in symptomatologie. Dit bleek niet het geval: het score-patroon op de vragenlijsten naar depressie kwamen sterk overeen voor vrouwen en mannen, zowel wat de losse vragen betrof als de groepen van bij elkaar horende vragen. Alleen op de vraag of men wel eens huilde, scoorden vrouwen wel en mannen niet. Vrouwen scoorden wel hoger op de meeste vragen.

Tenslotte werd de rol van risicofactoren voor depressie op oudere leeftijd onderzocht. Daarbij werden kleine verschillen gevonden in de kwetsbaarheid voor depressie, ten nadele van mannen. Dit betrof mannen zonder levenspartner, met een laag inkomen, en

met weinig emotionele steun: zij waren iets vaker depressief dan vrouwen in deze situaties. Echter het vóórkomen van diverse risicofactoren had een veel grotere invloed, en in dit geval ten nadele van vrouwen: vrouwen waren veel vaker zonder levenspartner, hadden veel vaker een laag inkomen en hadden veel vaker chronische, beperkende lichamelijke ziektes. Het netto resultaat hiervan was dat toch vooral vrouwen last hadden van de risicofactoren voor depressie bij ouderen, en dit draagt bij aan het vaker voorkomen van depressie bij vrouwen op oudere leeftijd.

In *hoofdstuk 3* komt de rol van de (christelijke) geloofsachtergrond ter sprake. Het is bekend dat geloof zowel een beschermende als een uitlokkende factor kan zijn voor depressie. Geloofsovertuiging heeft invloed op sociale en morele aspecten van het leven, en is een belangrijke culturele bron voor ouderen. Daarmee is geloofsovertuiging belangrijk voor de manier van omgaan met emoties, schuldgevoelens en verantwoordelijkheid, en kan bijdragen aan verschillen in voorkomen, symptomatologie en omgaan met depressie, en ook aan de man-vrouw-verschillen daarin.

In ons onderzoek bleek dat mensen met een protestantse geloofsovertuiging minder last hadden van depressie dan Rooms-Katholieken of niet-kerkelijken.

Binnen de depressieve groep hadden de protestanten meer last van geremdheid (niet op gang komen, alles kost moeite, minder spraakzaam) en lichamelijke klachten (slaapstoornissen, verminderde eetlust, concentratieproblemen) dan de andere twee groepen. Ook bij niet-gelovigen met één of twee protestantse ouders werd dit patroon gevonden. Deze verschillen bleken alleen bij de depressieve mannen aanwezig te zijn, maar niet bij de depressieve vrouwen.

In *hoofdstuk 4* is in vervolg op hoofdstuk 2 uitgebreider onderzoek gedaan naar de rol van sociale steun en depressie en het verband met sekse. Het ontbreken van sociale steun is een risicofactor voor depressie bij ouderen. Het gaat daarbij echter niet alleen om de hoeveelheid steun, maar ook om de kwaliteit, de betekenis en de impact van de steun, die, zoals genoemd, verschillend kunnen zijn voor vrouwen en mannen. Daarbij speelt ook het belang dat de oudere hecht aan het hebben van steun een rol.

In de eerste meting van LASA waren oudere mannen zonder levenspartner vaker depressief dan vrouwen zonder levenspartner. Het ontbreken van voldoende emotionele steun droeg bij aan deze samenhang bij mannen; niet bij vrouwen.

Daarnaast bleken deze oudere mannen zonder levenspartner vaker een depressie te krijgen dan vrouwen in de loop van de studie, waarbij het hebben van een klein sociaal netwerk een voorspeller was (bij mannen) van deze ongunstige ontwikkeling.

Een hoge behoefte aan sociaal-emotionele steun was geassocieerd met meer depressie bij vrouwen in de eerste meting, maar voorspelde niet een depressie in het beloop van de studie.

In een subgroep van ouderen met weinig sociale steun, in combinatie met een hoge behoefte daaraan, werden veel hogere percentages depressie gevonden, vooral bij mannen.

Deel 2: gebruik van psychofarmaca bij depressie bij ouderen

In de volgende drie hoofdstukken staat het gebruik van antidepressiva en benzodiazepinen (kalmeringsmiddelen en slaapmiddelen) centraal, met aandacht voor veranderingen daarin in de loop van de studie, voor de samenhang met depressie, en voor de verschillen tussen mannen en vrouwen.

In *hoofdstuk 5* is het gebruik van antidepressiva en benzodiazepinen in de eerste meting van LASA onderzocht. Hierbij werd gevonden dat slechts 5% van de mensen met een depressief syndroom antidepressiva gebruikten. Aangezien bij een lichtere vorm van depressie medicatie niet de eerste behandelvoorkeur is, werd daarnaast de groep met een ernstiger vorm van depressie, volgens de criteria van de DSM, apart onderzocht. In deze groep was het gebruik van een antidepressivum wel iets hoger, namelijk 16%, maar daarmee nog altijd erg laag. Naarmate men ouder was of meer cognitieve beperkingen had, was het antidepressiva-gebruik nog lager. Bovendien gebruikte nog niet de helft van deze mensen het antidepressivum in een voldoende dosering. Er waren geen aanwijzingen dat de ernstig depressieven zonder medicatie een andere therapie hadden, zoals psychotherapie. Opvallend was dat de depressieve mannen twee keer zo vaak een antidepressivum gebruikten als de depressieve vrouwen, n.l. 25% vs 14%. Benzodiazepinen werden door alle mensen met een depressie vaker gebruikt dan antidepressiva, waarbij vrouwen nu juist vaker deze middelen gebruikten dan mannen. Benzodiazepinen verhelpen de depressieve klachten niet, en kunnen zelfs leiden tot verergering van bepaalde depressieve symptomen, zoals de verlaagde stemming, concentratieproblemen en het tekort aan energie.

In *hoofdstuk 6* is vervolgens het verloop van het antidepressiva-gebruik in de jaren na de eerste meting onderzocht. In deze periode, na 1992, zijn in Nederland nieuwe antidepressiva geïntroduceerd, zoals de zogenaamde "SSRI's", die gemakkelijker toe te dienen zijn en

minder bijwerkingen hebben. Het gebruik van antidepressiva door volwassenen is daarmee fors toegenomen.

In onze studie is het antidepressiva-gebruik op de vier meetmomenten in de periode van 1992-2002 onderzocht bij de ouderen van 65-85 jaar. Hierbij werd een toename van het antidepressivagebruik gevonden in de groep met de ernstige depressie: van 15% in 1992 naar 30% in 2002, dus een verdubbeling van het gebruik. Opvallend was dat in de groepen met de lichtere vormen van depressie, de toename nog wat groter was, n.l. van 3% naar 12%, terwijl juist in deze groep het nut van antidepressiva niet vaststaat.

De toename was voornamelijk te verklaren door een sterke toename van het gebruik van de SSRI's; het gebruik van de andere antidepressiva bleef ongeveer gelijk.

Ook de voorgeschreven dosering was veel vaker adequaat; en ook dit kwam voornamelijk op het conto van de SSRI's.

Tenslotte liet het onderzoek zien dat de toename van het antidepressivumgebruik het sterkst was in de oudste groep, die daarmee de achterstand ten opzicht van de jongere ouderen inhaalde. Bij depressieve ouderen met bijkomende problemen, zoals cognitieve beperkingen en lichamelijke ziekten, bleef het antidepressivagebruik lager dan bij de ouderen zonder deze problemen.

In *hoofdstuk 7* wordt het gebruik van de benzodiazepinen in de periode vanaf de eerste meting onderzocht. In de negentiger jaren van de vorige eeuw nam de aandacht voor de negatieve gevolgen van (m.n. langdurig) benzodiazepine-gebruik toe, zoals de lichamelijke en geestelijke verslaving, en de bijwerkingen, met specifiek voor ouderen sufheid, verhoogd risico om te vallen en geheugenproblemen. Tevens nam de kennis toe over het behandelen van angst- en spanningsklachten, op een andere manier dan met kalmeringsmiddelen, en werden de behandelrichtlijnen aangepast. De verwachting was dan ook dat het gebruik van benzodiazepinen af zou nemen, en dan met name het langdurig gebruik, en het gebruik door ouderen.

Voor dit onderzoek werden de ouderen van 55-64 jaar uit LASA I (1992) vergeleken met dezelfde leeftijdsgroep uit LASA II (2002). Daarbij bleek dat het benzodiazepinegebruik niet veranderde, met in beide groepen een gebruik van 8%.

De meesten gebruikten het middel langer dan 1 jaar, en deze groep groeide zelfs licht (70% in 1992; 80% in 2002).

Ook de samenhang met bepaalde factoren veranderde niet: zowel in 1992 als in 2002 werden benzodiazepinen meer gebruikt door vrouwen, en bij mensen met lagere opleiding, lager inkomen, chronische lichamelijke ziektes en beperkingen, geheugenproblemen en depressieve klachten.

CONCLUSIE

In het laatste hoofdstuk van dit proefschrift (*hoofdstuk 8)* wordt een samenvatting van de belangrijkste bevindingen gegeven, gevolgd door methodologische overwegingen en beperkingen van de studie, het belang van de studie voor de klinische praktijk en theorievorming, en aanbevelingen voor de toekomst.

Dit onderzoek laat de diversiteit van depressie op oudere leeftijd zien, en de uitdagingen om de behandeling te verbeteren.

Geslacht en leeftijd hebben hun eigen unieke relatie met depressie, maar zijn ook van invloed op sociaal-culturele factoren die gerelateerd zijn aan het vóórkomen en ontstaan van depressie, zoals opleiding, inkomen, burgerlijke staat, geloofsovertuiging, sociaal netwerk en sociale steun. Deze factoren zijn niet gelijk verdeeld over mannen en vrouwen, en over de jongere en oudere ouderen. Al deze aspecten moeten worden meegenomen bij het diagnosticeren en behandelen van depressie op oudere leeftijd, en zijn ook van belang voor preventieve maatregelen.

Medicamenteuze behandeling van depressie op oudere leeftijd liet enige verbetering zien ten tijde van de studie, waarbij zeker de oudste ouderen profiteerden van het beschikbaar komen van de SSRI's. Toch is het antidepressivum-gebruik in de groep ouderen met ernstige depressieve klachten nog steeds erg laag. Benzodiazepinegebruik werd niet lager, ondanks de toegenomen kennis van de negatieve gevolgen van langdurig gebruik.

Hoewel zeker kanttekeningen kunnen worden geplaatst bij de opzet van de studie en de gebruikte onderzoeksmethoden, biedt LASA unieke mogelijkheden voor het ouderenonderzoek doordat alle groepen, ook de oudere mannen, goed vertegenwoordigd waren in de onderzoeksgroep. Hierdoor was vergelijking tussen mannen en vrouwen ook op hoge leeftijd mogelijk.

Voor de toekomst is van belang de inzichten in de diversiteit van depressie bij ouderen verder uit te breiden, bijvoorbeeld via (de al lopende) samenwerkingsprojecten in Europa en elders in de wereld op het gebied van bevolkingsonderzoek. Gedetailleerde kennis over verhoogd risico op depressie voor bepaalde groepen en op een ongunstig beloop van de depressie kan bijdragen aan het ontwikkelen van verfijnde diagnostiek, genuanceerde afweging van behandelmogelijkheden, en specifieke preventieprogramma's. Daarnaast is ook samenwerking met klinische studies nodig, om de kennis van bevolkingsonderzoek te koppelen aan kennis over diagnostiek, behandeling en beloop van ernstige vormen van depressie. Op die manier kunnen subtypen van depressie nader worden gedefinieerd en meer toegespitste programma's voor behandeling en terugvalpreventie worden ontwikkeld.

Dankwoord

Het LASA-onderzoek is een langlopend multidisciplinair proces, en dat geldt in zekere zin ook voor het tot standkomen van dit proefschrift. Hoewel het traject langer werd dan verwacht, was het daardoor ook mogelijk meer data in het onderzoek mee te nemen en te profiteren van de unieke longitudinale dataverzameling die in LASA is opgebouwd . Multidisciplinair is het ook zeker geweest, met de bijdragen van velen met wie ik al die tijd of voor een periode gezamenlijk optrok binnen LASA of elders op mijn andere werkplekken en prive. Ter afsluiting wil ik graag al die mensen bedanken.

Allereerst de deelnemers aan de LASA studie. Dank voor uw bereidheid om mee te werken aan de dataverzameling, nu al 30 jaar geleden gestart, en voor een aantal van u nog steeds een driejaarlijks terugkerend gebeuren: bezoek van een LASA-veldwerker die je het hemd van het lijf vraagt en divers lichamelijk onderzoek verricht, en daarnaast het invullen en terugsturen van een hele serie vragenlijsten. U heeft het mogelijk gemaakt om antwoorden te vinden op de vele vragen die bij de start van LASA werden gesteld en nog veel meer.

De leden van de beoordelingscommissie, prof. Bekker, prof. Gussekloo, dr Gijsbers van Wijk, prof. van der Mast, prof. Oude Voshaar en prof. van Tilburg wil ik graag bedanken voor de aandacht die zij aan mijn proefschrift hebben willen schenken.

Al tijdens mijn opleiding tot psychiater ontstond het verlangen om de klinische praktijk te combineren met wetenschappelijk onderzoek, en dan specifiek in de ouderenpsychiatrie en vanuit mijn nieuwsgierigheid naar achtergronden van man-vrouw verschillen in de psychiatrie. Van een algemeen idee naar concrete vraagstellingen, passend onderzoek en uiteindelijk publicaties en een proefschrift, is een lange en complexe weg, die ik niet had kunnen afleggen zonder de niet-aflatende steun van mijn begeleiders Aartjan Beekman, Dorly Deeg, Willem van Tilburg en Max Stek. Alle andere activiteiten, zoals de patiëntenzorg op de polikliniek, diverse taken in management en onderwijs, maar ook in mijn gezin, de kerk en mijn grote passie de muziek, belemmerden wel eens de voortgang van de wetenschap. Ik prijs me zeer gelukkig dat jullie altijd optimistisch zijn gebleven over het slagen van de onderneming, en jullie je steeds weer met interesse en zorgvuldigheid in mijn manuscripten verdiepten.

Aartjan Beekman, promotor, collega-psychiater en trouwe vriend! jij kent mij al heel lang, en ik bewonder de manier waarop je mij tijdens mijn promotietraject, zo enthousiasmerend en zuiver, hebt begeleid. Met je enorme kennis van de psychiatrie en de epidemiologie, je zicht

op de grote lijnen in combinatie met je goede oog voor detail, je creatieve en stimulerende commentaren op mijn ideeën en manuscripten in wording, heb je me geholpen om steeds de draad weer op te pakken. Van de discussies over de richting en de uitvoering van de onderzoeksvragen heb ik veel geleerd. Altijd was er ruimte voor overleg, ook toen je werkzaamheden steeds uitgebreider en veeleisender werden.

Dorly Deeg, onvolprezen 'baas' van LASA: onder jouw bezielende leiding is LASA uitgegroeid tot een (ook internationaal) toonaangevende onderzoeksgroep en zijn vele promotietrajecten succesvol verlopen, waaronder dus nu ook die van mij. De aandacht voor man-vrouw-verschillen is een gezamenlijke interesse en jij wist altijd weer dit aspect een goede plaats te geven in de verschillende artikelen. Ook kwam ik door jou in contact met binnenlandse en buitenlandse onderzoekers op dit gebied. Je hebt me laten profiteren van je grote kennis op het gebied van epidemiologie, en van onderzoeksmethoden en statistiek op dit terrein, iets waarin ik als doorsnee dokter weinig scholing in had. Ook wil ik je bedanken voor de grondigheid waarmee je mijn manuscripten van commentaar voorzag terwijl ik al dacht dat het nu wel goed was: altijd weer werden de artikelen er beter van.

Max Stek, met jouw aanstekelijke enthousiasme voor ons vak, waarbij je onderwijs, onderzoek en klinische patiëntenzorg combineert, ben je een voorbeeld voor mij en ik ben dan ook zeer verheugd dat jij nu als hoogleraar ouderenpsychiatrie mijn co-promotor bent. Onze paden kruisten elkaar geregeld. Ooit ben ik begonnen als co-assistent bij jou op de afdeling, later was ik arts-assistent en nu zijn we collega's in de ouderenpsychiatrie en ben ik plaatsvervangend opleider naast jou. Ik hoop na deze promotie nog lang met je te kunnen samenwerken op al die gebieden van de ouderenpsychiatrie, en te genieten van je gedrevenheid, je visie op het vak en je humor!

Willem van Tilburg, nestor van de (ouderen)psychiatrie, in allerlei fasen van mijn werkzame leven ben jij belangrijk geweest: eerst als voorzitter van de onderwijscommissie, later als mijn opleider en nu als begeleider en co-promotor bij mijn onderzoek. Ik ben je dankbaar voor je vertrouwen en je steun in die verschillende fasen en voor de stimulerende, vertrouwde sfeer die je op al die plekken wist te creëren. Je bracht de aandacht voor man-vrouw-verschillen in de praktijk door als één van de eerste opleiders een parttime traject mogelijk te maken, waar ik dankbaar gebruik van heb gemaakt als moeder van jonge kinderen. En ook al was je de laatste jaren officieel met emeritaat, altijd bleef je betrokken bij mijn promotietraject en ben je getuige van de afronding daarvan!

Naast de directe begeleiding heb ik genoten van de collega's en de sfeer bij LASA. Toen ik begon was dat nog op de O-gang in het Wis- en Natuurkunde gebouw van de VU. Een warm bad, waarin de wetenschappelijke nieuwsgierigheid samen met een kritische houding centraal stonden. De samenwerking met collega's uit andere terreinen dan de geneeskunde heeft mij veel gebracht op gebieden als onderzoeksmethodieken, statistiek en sociologie/gerontologie. Ik kon zomaar instappen in LASA. Andere onderzoekers waren wel eens jaloers dat ik de beschikking kreeg over zo'n fantastische dataverzameling met daarbij inbegrepen de bijstand van deze onderzoeksgroep voor raad en daad. Dank aan alle LASA-medewerkers met wie ik in de periode van mijn onderzoek heb mogen samenwerken. Een aantal wil ik graag met name noemen, maar ook vele anderen hebben mij in het traject een stukje verder geholpen.

Hannie Comijs, wij kenden elkaar al door je werkzaamheden als neuropsycholoog op de ouderenpoli, en ik ben je dankbaar voor je co-auteurschap en het kritisch lezen van diverse artikelen, onze gezamenlijke inspanning voor de medicatie-data in LASA en je rol als trekker van AMSTAD en NESDO. Ik hoop dat ik vanuit de poli ouderen in de toekomst verder met je kan samenwerken in NESDO.

Arjan Braam, jij bent eerste auteur van één van de artikelen van mijn proefschrift, en niet toevallig gaat dat over religie, een onderwerp dat ons zowel wetenschappelijk als persoonlijk bezighoudt. Ook jou ben ik zeer dankbaar voor je tijd en je kennis die je zonder terughoudendheid met mij wilde delen. In mijn eerste LASA-jaar heb jij me geholpen om thuis te raken in de analysemethoden en statistiek in de grote en complexe data-verzameling van LASA en ook in de jaren daarna kon ik altijd bij je terecht met vragen. Je betrok mij bij EURODEP, het unieke samenwerkingsproject met een aantal andere bevolkingsstudies in Europa waarin jij op je eigen gedisciplineerde en charmante wijze de leiding nam vanuit Nederlandse zijde. Nu ben je hoogleraar op een plek die helemaal bij je past, en ik hoop dat we in de toekomst onze samenwerking op wetenschappelijk gebied kunnen voortzetten.

LASA dreef en drijft op een solide en stimulerende kerngroep voor het hele proces van ontwerp en uitvoering van het onderzoek, statistiek, databeheer, veldwerk en secretariële ondersteuning; een ijzersterk fundament. Vanaf mijn start in LASA kon ik profiteren van deze professionele infrastructuur, onontbeerlijk voor mij om thuis te raken in de complexe materie van LASA en van grootschalig epidemiologisch onderzoek.

Jan Smit, dank voor je enorme kennis van het ambacht van wetenschappelijk onderzoek doen, die je met de onderzoekers deelde op een heldere en kritische manier. Je beschikt over een scherp analytisch vermogen, of het nu gaat over data en onderzoek, of over medewerkers en de samenstelling van onderzoeksgroepen. In combinatie met je nuchtere Amsterdamse manier van doen heb je een breed gedragen gezag verworven. Van LASA ging je naar NESDA en nu in de Academische Werkplaats van GGZ inGeest, waarin ik vanuit de academische tak van de ouderenpsychiatrie weer van al jouw kennis, inzicht en humor mag profiteren!

Jan Poppelaars, vanaf het begin beheer jij al de data van LASA, en zorg je ervoor dat de systematiek en documentatie op orde is. We hebben heel wat uurtjes gestoken in de medicatie-data, complex zowel qua methode van verzamelen en opslaan in LASA zelf, als door de veranderingen in de landelijke systematiek in de loop van de tijd. Jij ging altijd weer met goede moed aan de slag om oplossingen te vinden, en daardoor is het niet alleen mogelijk geweest deze data in mijn proefschrift een centrale plaats te geven, maar zijn ze ook beschikbaar voor diverse andere onderzoekers binnen en buiten LASA. Veel dank voor je doorzettingsvermogen, én je geduld als ik weer eens een periode minder beschikbaar was voor LASA door al mijn andere werkzaamheden. En ik weet dat er nog vragen liggen betreffende nieuwe metingen en longitudinale documentatie…

Mariëtte Westendorp en Marleen van der Horst, jullie deden en doen de coördinatie van het veldwerk, en zonder jullie niet-aflatende inspanningen daarvoor had ik nooit zulke mooie data kunnen gebruiken voor mijn onderzoek. Dank voor jullie nauwgezette werkwijze, en de gezelligheid in de veldwerkkamer !

En natuurlijk bedank ik de secretaresses van LASA, dank zij wie LASA zowel binnen de groep als naar buiten toe een geoliede machine is. In het bijzonder wil ik Fadime Kursun noemen: dank voor je jarenlange gedegen inzet voor LASA, het nasturen van mijn post als ik weer eens langere tijd niet op LASA was, je gezelligheid en gastvrijheid (fantastische Turkse lekkernijen op het secretariaat en een zomerse barbecue-avond in je tuinhuis) en je belangstelling en vertrouwen, ook in de persoonlijke sfeer.

Theo van Tilburg, jij stond met NESTOR-LSN, de voorloper van LASA, aan de wieg van al dit mooie onderzoek. Bij de colloquia van LASA heb ik van jou geleerd dat wetenschapsmethodiek en statistiek niet objectief en zwart-wit zijn, maar dat ook daarin

bepaalde keuzes moeten worden gemaakt en overdacht. Jouw kritische inslag, grote kennis van de methodologische en statistische kanten van onderzoek, en je mooie data betreffende sociale netwerken, steun en eenzaamheid, hebben mij geholpen bij het tot stand komen van diverse artikelen, en natuurlijk specifiek van het artikel over sociale steun waarvan jij mede-auteur bent.

Cees Jonker, kamergenoot op LASA, maatje op de polikliniek, en ook nog dorpsgenoot: ik heb genoten van onze gesprekken over al die gezamenlijke interessegebieden. Altijd opgewekt en op zoek naar nieuwe mogelijkheden, stimulerend en tegelijk wijs en kritisch vanuit je enorme ervaring op het toen nog onontgonnen gebied van de gedragsneurologie. Wij schreven samen een handzaam artikel over agitatie bij dementie, en jij legde de basis voor ketenzorg dementie in Amsterdam en voor het zorgprogramma cognitieve stoornissen zoals dat nu binnen het ouderencircuit van GGZ inGeest is opgesteld.

Iris Vrieling, mijn eerste kamergenote op LASA: jij voerde mij mee in de wereld van de Mokken analyse, een onderdeel van mijn eerste publicatie.

Marja Aartsen, Sandra Geerlings, Miranda Dik en Mirjam Geerlings, jullie waren mijn collega's in mijn begintijd bij LASA. Ik heb veel van jullie geleerd op gebied van onderzoek en niet-zieke ouderen, en genoten van jullie gezelligheid.

Suzan van de Pas, wij deelden een poosje de kamer, en met jouw achtergrond als verpleegkundige van Opname Ouderen, ook onze liefde voor het klinische werk met de patiënten.

Ellis Bierman en Dagmar Vink, dank voor jullie mede-auteurschap, en jullie bijdrage aan onderdelen van LASA die van belang zijn geweest voor dit proefschrift: Ellis, jouw gedegen verdieping in de benzodiazepines, en Dagmar, jouw mooie longitudinale dataset, dank dat ik daarvan gebruik heb mogen maken.

Brenda Penninx, als een wervelwind kwam je langs LASA toen ik daar zat. Je was al gepromoveerd, kwam vanuit Amerika, en ging na korte tijd LASA weer naar Amerika, en toen naar NESDA. Je was iedereen een stap voor met je ideeën én met de uitvoering daarvan. Dank voor jouw scherpzinnige bijdragen aan de colloquia en teamvergaderingen.

Robert Schoevers, maatje vanuit de opleiding, en later gezamenlijk in het epidemiologisch

onderzoek, beiden zoekend naar de afstemming met het klinische werk, dat altijd aan je trekt, en het gezinsleven inclusief ambitieuze levenspartner. Dank voor je gezelligheid en de vertrouwdheid, die nog steeds aanwezig is, ook nu je verder weg in Groningen zit, met je prachtige aanstelling als hoogleraar.

Willeke van Zelst, net als Cees Jonker en Robert Schoevers ben jij voor mij een maatje zowel in mijn klinische werk als in onderzoek, en delen wij ook nog onze interesse voor onderwijs en opleiding. Na al een korte samenwerking in mijn tijd als onderwijs-coördinator psychiatrie, werd jij mijn supervisor tijdens de keuzestage ouderenpsychiatrie in het Slotervaart Ziekenhuis, waar ik onder jouw bezielende leiding en onnavolgbare inzet de eerste stappen zette in de ouderenpsychiatrie. De hoeveelheid werk die jij verzette en het tempo van werken (en praten en lopen) zijn legendarisch geworden, en maakten korte metten met het idee dat ouderenpsychiatrie een traag vak zou zijn waarin nooit iets gebeurt. Dankzij de combinatie van je harde werken met je brede interesse, aandacht voor je collega's, ook op het persoonlijke vlak, en goede organisatievermogen, werd de 'poli Elba' zoals de geuzennaam luidde, een sterk, productief en zeer gewaardeerd onderdeel van de instelling. Ook jij deed onderzoek bij LASA, en gelukkig voor mijn zelfbeeld lukte het jou ook niet altijd om de afgesproken tijd vrij te maken bij alle hectiek van patiëntenzorg en management. Via jou kwam ik in de ouderenpsychiater-intervisiegroep, waar jij helaas moest afhaken na je vertrek naar Groningen. Ook ons persoonlijk contact, deels via de contacten van onze kinderen, die van jouw zus, en jouw zus zelf, is mij zeer dierbaar.

Dank ook Marijke van ter Toolen en de andere medewerkers van de bibliotheek, voor het aanleveren van de literatuur en de snelle hulp bij de searches, ook toen dat nog niet allemaal zo gemakkelijk digitaal kon.

Jaap Couvee, vriend van de zeilkampen en maatje in de muziek van weleer, onze paden kruisten elkaar jaren later in de psychiatrische wetenschap, en dank zij jou kwam er een grant waar ik weer een poosje mee verder kon. Dank daarvoor!

Ondertussen ben ik aangeland bij mijn andere werkplekken gedurende de periode van het LASA-onderzoek. De collega's met wie ik de afgelopen jaren heb gewerkt, hebben wel gezien dat het niet altijd mee viel om mijn tijd goed te verdelen en de tijd te nemen die nodig is om je te verdiepen in de data-analyse en het schrijven van de artikelen. Velen hebben mij gesteund zodat ik steeds de draad weer oppakte. Jullie vertrouwen dat ik het kon, en jullie

daadwerkelijke steun om de patiëntenzorg tijdelijk aan anderen over te laten, hebben mij enorm geholpen om het promotietraject af te ronden en het niet halverwege op te geven.

Piet Eikelenboom, jouw overtuiging dat het beste onderzoek wordt gedaan als de onderzoeker met het andere been in de kliniek en de dagelijkse praktijk van de patiëntenzorg staat, in combinatie met de geruststelling dat het niet op een paar maanden (of jaren!) meer of minder aankomt, hebben mij steeds geholpen om rustiger verder te gaan. Het is een voorrecht om in jouw stimulerende spoor door te gaan in 'ons' Ouderencircuit, en gelukkig ben je nog steeds vaak genoeg aanwezig om ons te laten profiteren van je enorme kennis van praktijk en wetenschap, je scherpe blik en de vertrouwde wijze waarop je het onderwijs educatief op een hoger plan trekt.

Mijn collega-specialisten op de polikliniek Paul David Meesters, Annemieke Dols en Jeroen de Jong: een echt 'dreamteam', ik kan me niet beter wensen! Ik hoop nog heel lang met jullie samen te werken, op al die vlakken van patiëntenzorg, wetenschap, onderwijs en opleiding, en met natuurlijk onze gezellige etentjes!

Paul David, al jaren collega-psychiater, eerst in het Slotervaart Ziekenhuis en later op de Polikliniek Ouderen Zuid, waar ik nu, na jou, ook de manager zorg ben. En eindelijk, net als jij, nu een proefschrift! Ik geniet van onze prettige en vruchtbare samenwerking. Jouw sociaal-psychiatrische achtergrond en je ervaring in de consultatieve sector betekenen voor mij een verrijking en verdieping van ons werk op de poli, en van meet af aan heb ik me vertrouwd gevoeld bij jouw kritisch-bewogen collegialiteit, je inzet voor verbetering van de patiëntenzorg voor kwetsbare groepen in de samenleving, én je aandacht voor het wel en wee van de medewerkers en de samenwerking op de poli.

Annemieke, met je komst naar onze poli heb je het nest goed opgeschud! Je creativiteit en je vermogen om onderzoeksvragen te koppelen aan de werkvloer, en daar allerlei mensen voor te vinden om ze uit te voeren, je enthousiasme, grote inzet, betrokkenheid en kritische inslag zijn een heerlijke aanvulling voor onze poli, en van grote waarde voor het gehele ouderencircuit. Je bent erg goed in strategisch denken en zaken systematische opzetten en uitvoeren, en daarbij een fijne en gezellige collega. Ik ben heel blij dat je mijn paranimf bent, en kan zelfs mijn controlebehoefte grotendeels opzij zetten!

Jeroen, ook jij bent al lang een vertrouwde en zeer gewaardeerde collega. Tijdens mijn opleiding kwam ik je al tegen bij het RIAGG-overleg, door jullie het VK-overleg genoemd,

en het was me toen al duidelijk dat ik graag met je zou willen werken . Je degelijke werkwijze, je grote kennis en ervaring in de psychogeriatrie, je genuanceerde oog voor de patiënt en zijn systeem zijn van grote waarde voor de poli. Je gevoel voor humor en voor taal zijn een genot!

Dankzij ons fantastische secretariaat loopt de poli gesmeerd. Ondanks alle drukte van de afgelopen jaren met bezuinigingen, reorganisaties, verhuizingen en wat al niet, bleef er daardoor bij mij energie over om me steeds weer op het onderzoek te richten. Dank Annemieke Westenberg, Hannie Spel, Natasha Girwar en Pia Verheul, en allen die eerder op het secretariaat werkten!

Gert Jan Kesseler, mijn duale maatje op de poli, dank voor de samenwerking, en de ruimte die je mij geeft in al het werk dat jij op je neemt. Ook de verdere collega's van de polikliniek wil ik bedanken voor hun bijdrage aan onze fijne poli. Een gouden plek, heerlijk om met jullie te werken.

Dat geldt ook voor de andere collega's van het ouderencircuit. Didi Rhebergen, Eric van Exel, Sigfried Schouws, Cora Kerssens, Daniel van Grootheest, en eerder ook Marijke Bremmer en Frits van der Wurff, jullie gang op het wetenschappelijke pad stimuleerde mij zeker om door te gaan! Medepsychiaters en specialisten ouderengeneeskunde en managers van het Circuit Ouderen in Amsterdam, en later ook breder met Amstelveen en Haarlem, dank voor de fijne samenwerking.

Audrey van Schaik en Jan Willem Pijpers, dank voor jullie vertrouwen in mij en jullie vaardige en deskundige besturing van ons circuit; in deze hectische tijden geen gemakkelijke taak.

Ineke van Keeken, collega's van de poli psychiatrie in het Slotervaart, en de geriaters van het Slotervaart en het COGA, dank voor jullie hulp en collegialiteit in de afgelopen jaren!

Ook aan mijn familie en vrienden is het langgerekte traject niet ongemerkt voorbij gegaan. Mijn dames van het LVC, mijn vriendinnen van school en studie: jullie hebben meegeleefd, hadden er soms wat last van, maar ook weer niet te veel, want ik kon het niet laten om de wetenschap even opzij te zetten voor allerlei leuke gelegenheden en activiteiten. En ik heb daar ook van genoten!

Mijn medezangers van onze 'zangclub' en mijn quatre-mains-maatje José, dank voor jullie meeleven en of ik het nu echt rustiger krijg is natuurlijk de vraag… ik weet vast wel weer iets te vinden om de drukte erin te houden. Maar zeker ga ik mijn geliefde hobby de muziek een ruimere plaats geven, en dat natuurlijk graag met jullie samen!

Lieve ouders, vanaf dat ik heel jong was hebben jullie ervoor gezorgd dat ik mij kon ontwikkelen en ontplooien op diverse terreinen. Jullie liefde en vertrouwen, jullie belangstelling voor mijn werk, en jullie praktische hulp zoals het vele oppassen op de kinderen, de hulp in tuin en huis, en het meedenken bij belangrijke beslissingen, heeft mij ver gebracht, en daar ben ik jullie heel dankbaar voor. Ik ben er trots op dat jullie mijn promotie mogen meemaken en ik dit boekje aan jullie op kan dragen!

Lieve kinderen, jullie zagen mij vele uren achter de computer zitten, en vooral Marjolijn zat mij ook geregeld achter de vodden: 'Is dat boek nu nog niet af?' En ja, nu is het af!

Eveline, grote oudste dochter, jij hebt je blijkbaar niet laten afschrikken, want je bent niet alleen dokter geworden, maar je wilt ook psychiater worden en dan zelfs nog in de ouderenpsychiatrie met een academische invulling. Als klein meisje was je al een doorzetter, al kon je wel eens twijfelen of je wel kon voldoen aan wat blijkbaar normaal was in ons gezin. Je hebt je ontwikkeld tot een veelzijdige, breed geïnteresseerde jonge vrouw, een enorm harde werker, met daarnaast ook ruimte en oog voor sociale kanten van het leven, hechte vriendschappen, en je fijne relatie met je geliefde Jelle. Je hebt je zaken altijd tiptop in orde, met goede planning en voortvarende uitvoering. Ik vind het geweldig leuk dat jij mijn paranimf bent, en laat met een gerust hart de organisatie over aan jou en Annemieke!

Tijmen, veelzijdige zoon, het was een genot om te zien wat er uit het dromerige mannetje is gegroeid in de afgelopen jaren. Met je grote leervermogen, je heerlijke muzikaliteit en je vriendelijke aard, waarbij je gelukkig niet over je laat lopen, heb je je eigen bijzondere plaats in ons gezin, bij je geliefde Margot en haar familie en in je vriendenkring. Dat het verstrooide er niet helemaal afgegaan is, ach, dat houdt het spannend!

En Marjolijn, onze benjamin, en als baby de temperamentvolste van de drie, ook jij bent al een grote tiener, en laat ons genieten van je gezelligheid, je leuke vriendinnen, je sportiviteit en je muzikale talenten. Als een echt kind van je tijd, weet je veel meer van de digitale wereld, waar ik weer een graantje van kon meepikken voor mijn presentaties, het bewerken van foto's en wat er verder maar handig was voor mijn werk of regelzaken.

En ja, geliefde Dick, wat prijs ik me gelukkig met jou naast mij! Altijd was jij ervan overtuigd dat ik dit onderzoekstraject tot een goed einde zou brengen, ook als ik het zelf niet meer zo goed wist. Dank je wel voor je stimulans en vertrouwen, en voor je praktische hulp bij de teksten en het Engels. Dank ook voor de ruimte die ik van je kreeg om eerst de opleiding te kunnen doen naast ons gezin, en later tijd en energie te kunnen steken in het onderzoek en mijn andere veeleisende werkzaamheden. Gelukkig wisten we toch altijd ook nog tijd te maken voor de andere belangrijke zaken: het gezin, de muziek, lekker samen eten. En daar ga ik graag zo lang mogelijk mee door, met jou samen!

Curriculum Vitae

Curriculum Vitae

Caroline Margaretha Sonnenberg werd geboren op 23 januari 1960 in Ouderkerk aan de Amstel. Na het behalen van het Gymnasium-β diploma aan het Hermann Wesselink College te Amstelveen begon zij in 1978 met de studie Geneeskunde aan de Vrije Universiteit van Amsterdam. Tijdens de studie was zij actief binnen het mentoraat en maakte zij met een groep medestudenten en docenten een studiereis naar Boedapest, toen nog achter het IJzeren Gordijn, met als doel het bezoeken van enkele ziekenhuizen en kennisuitwisseling met Hongaarse collega's. Naast de studie deed zij veel aan muziek (piano en zang) en was zij begeleider bij zeilkampen voor middelbare scholieren.

Na het behalen van het artsexamen in 1987 werkte zij enkele maanden als arts-assistent geriatrie in het Slotervaart Ziekenhuis in Amsterdam, als vervolg op een keuze-coschap aldaar. Daarna ging zij voor een periode van anderhalf jaar naar Roermond, waar zij werkte als arts-assistent gynaecologie in het St. Laurentius Ziekenhuis. Op beide plekken werd zij bevestigd in haar enthousiasme voor de combinatie van psychiatrie en somatiek, en wel specifiek bij de oudere patiënt.

In 1989 volgde de stap naar de psychiatrie, in de Valeriuskliniek, voorloper van GGZ inGeest. De eerste vier jaar was zij werkzaam als onderwijscoördinator bij de vakgroep psychiatrie van de VU, waar zij in nauwe samenwerking met Jaap Veldkamp en de andere leden van de onderwijscommissie een bijdrage kon leveren aan nieuwe ontwikkelingen en professionalisering van het psychiatrie-onderwijs binnen de studie geneeskunde van de VU. Hier is ook de bodem gelegd voor de liefde voor het onderwijs. In 1993 kwam zij in opleiding in de Valeriuskliniek bij prof dr W. van Tilburg. Aansluitend aan de basisopleiding volgde zij een keuzejaar Ouderenpsychiatrie. De stage was een combinatie van patiëntenzorg op de polikliniek psychiatrie in het Slotervaart Ziekenhuis, onder de bezielende leiding van Willeke van Zelst, en wetenschappelijk onderzoek bij LASA, onder de deskundige hoede van Dorly Deeg en haar team. Na het afronden van de opleiding in 1998 zette zij als psychiater deze combinatie voort, met een kleine aanstelling bij LASA, die dankzij aanvullende financiering vanuit LASA, de vakgroep psychiatrie en de industrie een aantal keren kon worden verlengd. Daarnaast kreeg zij een aanstelling als ouderenpsychiater bij het Ouderencircuit van GGZ inGeest (toen nog Psychiatrisch Centrum Amsterdam en later GGZ Buitenamstel geheten). Zij werkte ruim drie jaar als vaste consulent psychiatrie bij de afdeling geriatrie van het Slotervaartziekenhuis. Eind 2001 stapte zij over naar de Ouderen- en Geheugenpolikliniek aan het Valeriusplein, dat enkele jaren later samen met het Ambulante

Wijkteam Ouderen Zuid verder ging als Polikliniek Ouderen Zuid. Naast patiëntgebonden werkzaamheden kreeg zij taken op het gebied van onderwijs, opleiding en in de groeiende samenwerking met het Alzheimer Centrum en de Interne Ouderengeneeskunde van het VUmc. Sinds enkele jaren is zij ook manager zorg binnen de polikliniek.

Caroline is getrouwd met Dick Veltman. Zij hebben drie kinderen: Eveline, Tijmen en Marjolijn.

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